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Medical Policy Manual

Topic: Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. 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. 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.

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

It has been proposed that various apo E genotypes are more atherogenic than others and that apo E measurement may provide information on risk of CAD above traditional risk factor measurement. It has also been proposed that the apo E 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. Apo E genotype may be one factor that determines an individual's degree of response to interventions such as statin therapy.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

A 2002 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment[1] summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor […] independently contributes to risk assessment compared to established risk factors.
- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Similarly, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) guidelines document notes that, to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:[2]

- 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.

The focus of the following literature appraisal is on evidence related to the ability of apo E testing to

- Provide clinically relevant information beyond that provided by traditional lipid measures, and
- Improve health outcomes as a result of patient management decisions that would not otherwise have been made in the absence of apo E testing.

Literature Appraisal

Apo E as a Predictor of Cardiovascular Disease

A large body of research has established a correlation between lipid levels and the underlying apo E genotype. Numerous studies have focused on the relationship 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.[3-8] These studies have generally shown a relationship between apo E and these surrogate outcomes. For example, in population studies, the presence of an apo e2 allele was associated with the lowest cholesterol levels and the apo e4 allele was associated with the highest levels.[9,10] Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of total and LDL-cholesterol levels.[11-14]

Some larger observational studies have correlated apo E genotype with clinical disease. For example, the Atherosclerosis Risk in Communities (ARIC) study followed 12,000 middle-aged individuals free of coronary artery disease (CAD) at baseline for 10 years.[15] This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik et al. reported that apo E polymorphisms were associated with LDL levels and carotid intima-media thickness but were not predictive of incident CAD.[16]

A 2007 meta-analysis published by Bennet and colleagues summarized the evidence from 147 studies on the association of apo E genotypes with lipid levels and cardiac risk.[17] Eighty-two studies included data on the association of apo E with lipid levels, and 121 studies reported the association with clinical outcomes. The authors reported the following findings:

- Patients with the apo e2 allele had LDL levels that were approximately 31% less compared with patients with the apo e4 allele.
- Patients with the apo e3 allele had an approximately 20% decreased risk for coronary events compared with patients with apo e2 (OR: 0.80; 95% CI: 0.70–0.90).
- Patients with the apo e4 had an estimated 6% higher risk of coronary events that was of marginal statistical significance (OR: 1.06; 95% CI: 0.99–1.13).

No studies were identified that compared the health outcomes of patient management based on apo E genotypes compared with patient management based on conventional risk assessment measures such as LDL. Therefore, it is unclear how the associations reported above can be used to improve health outcomes over current patient management procedures.

Apo E as a Predictor of Response to Therapy

ApoE 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.[18,19] Other studies have suggested that response to statin therapy may vary with apo E genotype and that the e2 allele indicates greater responsiveness to statins.[18,20] The following are examples of currently published studies.

- Chiodini et al. examined differential response to statin therapy according to apo E genotype by reanalyzing data from the GISSI study.[21] GISSI was a randomized controlled trial (RCT) comparing pravastatin with placebo in 3,304 Italian patients with previous myocardial infarction (MI). Patients with the apo e4 allele treated with statins had a greater response to treatment as evidenced by lower overall mortality (1.85% vs. 5.28%, respectively, p=0.023), while there was no

difference in mortality for patients who were not treated with statins (2.81% vs. 3.67%, respectively, p=0.21). This study corroborates results reported in previous studies but does not provide evidence to suggest that changes in treatment should be made as a result of apo E genotype.

- Donnelly et al. reported on 1,383 patients treated with statins from the Genetics of Diabetes Audit and Research in Tayside, Scotland (Go-DARTS) database.[22] The researchers reported on the final LDL levels and percent of patients achieving target LDL according to apo E genetic status. LDL levels following treatment were lower for patients who were homozygous for apo e2, compared to patients homozygous for apo e4 (0.6 +/- 0.5 mmol/L vs. 1.7 +/- 0.3 mmol/L, p<0.001). All patients who were homozygous for apo e2 reached their target LDL level, compared to 68% of patients homozygous for apo e4 (p<0.001).

- Vossen et al. evaluated response to diet and statin therapy by apo E status in 981 patients with CAD who were enrolled in a cardiac rehabilitation program.[23] These authors reported that patients with an apo e4 allele were more responsive to both diet and statin therapy than were patients with an apo e2 allele. The overall response to treatment was more dependent on baseline LDL levels than apo e genetic status, with 30–47% of the variation in response to treatment explained by baseline LDL, compared to only 1% of the variation explained by apo E status.

No studies were identified that directly compared the treatment plans and health outcomes of patient management that was based on apoE status with those based on conventional lipid measures.

Clinical Practice Guidelines and Position Statements

No clinical practice guidelines or position statements from U.S. professional associations were identified that recommended the use of apo E in cardiovascular risk assessment, including but not limited to the following:

- The 2010 American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk in asymptomatic patients.[24]
- The 2009 U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease.[25]
- The 2001 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) position statement for cardiovascular risk assessment.[2]
- The American Diabetes Association and the American College of Cardiology Foundation consensus conference publication.[26]

Summary

<u>Apo E as a Predictor of Cardiovascular Disease</u>

The current evidence suggests that, while apolipoprotein E (apo E) genotype may be associated with lipid levels and coronary artery disease (CAD), it is considered a relatively poor predictor of CAD and is unlikely to provide additional clinically relevant information beyond traditional lipid measures such as low density lipoprotein (LDL). Moreover, apo E has not been incorporated into standardized cardiac risk assessment models. Therefore, the use of apo E measurements is considered investigational in the risk assessment and management of cardiovascular disease.

Apo E as a Predictor of Response to Therapy

The current evidence suggests that apolipoprotein E (apo E) genotype may be a predictor of response to statins and may allow clinicians to better gauge an individual's chance of successful treatment. However, not all studies are consistent in reporting this relationship. At present, it is unclear how the information provided by apo E testing will change clinical management or impact patient health outcomes. Dietary modifications are a universal recommendation for those with elevated cholesterol or low density lipoprotein (LDL) levels, and statin drugs are the overwhelmingly preferred agents for lipid-lowering therapy. It is unlikely that a clinician will choose alternative therapies, even in the presence of an apo E phenotype that indicates diminished response. Given the uncertain impact on clinical outcomes, apo E testing is considered investigational as a predictor of response to lipid-lowering therapy.

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CROSS REFERENCES

Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk. Laboratory, No. 63

CODES	NUMBER	DESCRIPTION
CPT	81401	Molecular pathology procedure, Tier 2, Level 2
HCPCS	None	