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Medical Policy Manual

Topic: Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment

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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

Lipoprotein(a) (LPA) is a lipid-rich particle similar to low-density lipoprotein (LDL) and has been determined to be an independent risk factor for coronary artery disease (CAD). Patients with a positive test for the LPA genetic variant rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin. As a result, testing for the rs3798220 variant has been proposed as a method of stratifying benefit from aspirin treatment.

A large amount of epidemiologic evidence has determined that LPA blood level is an independent risk factor for cardiovascular disease. The overall degree of risk associated with LPA levels appears to be modest, and the degree of risk may be mediated by other factors such as LDL levels and/or hormonal status.

Levels of LPA are relatively stable in individuals over time but vary up to 1,000-fold between individuals, presumably on a genetic basis. A single nucleotide polymorphism (LPA rs3798220) has been identified in the LPA gene that has been associated with both elevated levels of lipoprotein(a) and an increased risk of cardiovascular disease. Mendelian randomization studies have supported the hypothesis that these genetic variants, and the subsequent increase in LPA levels, are causative of cardiovascular disease.

Aspirin is a well-established treatment for patients with known coronary artery disease (CAD). It is also prescribed as primary prevention for some patients who are at increased risk of CAD. Current recommendations for primary prevention consider the future risk of cardiovascular events weighed against the bleeding risk of aspirin. U.S. Preventive Services Task Force (USPSTF) guidelines[1] from 2009, and updated in 2013, recommend aspirin for men between the ages of 45-79 years when the benefit in reducing myocardial infarction (MI) exceeds the risk of bleeding, particularly gastrointestinal hemorrhage; and for women between the ages of 55-79 years when the benefit in reducing stroke exceeds the risk of gastrointestinal bleeding. Given guidelines such as these that recommend individualizing the risk/benefit ratio of aspirin therapy, additional tools that would aid in better defining the benefits of aspirin, and/or the risk of bleeding, have potential utility for clinicians who are making decisions on aspirin therapy.

LPA-Aspirin Check® is a commercially available genetic test (Berkeley HeartLab) that detects the presence of the rs3798220 allele. DNA is extracted from a buccal swab sample taken from the inner cheek. Genetic testing is performed by real-time polymerase chain reaction (PCR) in conjunction with several control samples.[2] Real-time PCR is expected to be more accurate than traditional PCR, since it preserves the exquisite sensitivity of PCR, while reducing the probability of cross-contamination that can result in false-positive results.[3] According to these authors, the main limitations to real-time PCR accuracy are human factors such as improper assay development, incorrect data analysis, or unwarranted interpretation.

Patients with a positive test for rs3798220 have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin. It has been proposed that the additional information obtained from the LPA-Aspirin Check test may aid physicians in better estimating the benefit/risk of aspirin therapy and therefore may aid in deciding whether to prescribe aspirin for individual patients.

MEDICAL POLICY CRITERIA

The use of genetic testing for the rs3798220 allele (LPA-Aspirin Check®) is considered **investigational** in patients who are being considered for treatment with aspirin to reduce risk of cardiovascular events.

SCIENTIFIC EVIDENCE

Genetic testing for the LPA rs3798220 can be evaluated in a similar framework as other novel cardiac risk factors. There are several conditions that must be met in order for a cardiovascular risk factor to demonstrate clinical utility. A 2002 TEC Assessment[4] summarized three steps necessary for clinical utility:

- Standardization of measurement of the risk factor.
- Determination of its contribution to risk assessment. It is important to determine how this novel risk factor compares to other known risk factors of a condition when assessing risk.
- Determination of how the novel risk factor 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 outcomes.

Literature Appraisal

Standardization

Is the measurement of the LPA rs3798220 allele standardized?

There were no published studies identified that evaluated the accuracy of real-time PCR testing for the specific rs3798220 allele. According to the manufacturer's website,[2] "The Real-Time PCR assay is extremely reproducible and has been validated for LPA genotyping by testing over 1,000 specimens from patients whose LPA status was already known. The test accuracy was 100% in validation studies."

Conclusion

This limited information is sufficient to conclude that real-time PCR is an accurate method for identifying genetic polymorphisms such as the rs3798220 allele, but it is not sufficient to conclude that the measurement of LPA rs3798220 is standardized.

Contribution to Risk Assessment

Is LPA rs3798220 an independent risk factor for coronary artery disease?

Several observational studies have evaluated whether LPA rs3798220 is an independent risk factor for coronary artery disease (CAD).

- Shiffman et al.[5] used data from the Cardiovascular Health Study, a prospective cohort study of risk factors for myocardial infarction (MI) in 4,522 individuals who were 65 years or older, to examine the association of rs3798220 with MI. These authors tested 74 single nucleotide polymorphisms (SNPs) that had been genotyped as part of the Cardiovascular Health Study. After 13 years of follow-up, 539 patients (12%) had developed MI. There were 8 SNPs that were independent predictors of MI, with hazard ratios (HRs) varying from 1.13-1.62. The rs3798220 variant was one of the independent predictors and had the highest HR (1.62 95% confidence interval [CI]: 1.09-2.42). The authors also calculated the false-positive reporting rate for each SNP and estimated this to be 1% for rs3798220.

- Clarke et al.[6] used a case-control design to examine the association of rs3798220 with CAD in 3,145 case patients and 3,352 control subjects from 4 European countries. They initially examined 48,742 SNPs in 2,100 genes that had some association with heart disease, including 40 SNPs from the lipoprotein(a) (LPA) gene. The rs3798220 SNP was found in 2% of patients and had the strongest association with CAD, with a HR of 1.92 (95% CI: 1.48-2.49). This association was then replicated in 3 independent populations from cohort studies, with a total of 4,846 case patients and 4,594 controls. In these populations, the rs3798220 variant remained an independent risk factor for CAD, with an odds ratio (OR) that was somewhat lower than in the derivation population (OR: 1.68 95% CI: 1.43-1.98).

- Luke et al.[7] examined the association of SNPs with severe CAD as determined by coronary angiography. These authors used populations from 3 case control studies in sequence to determine the SNPs that were most strongly associated with severe CAD. Starting with over

12,000 SNPs, the authors identified 302 SNPs associated with severe disease; following verification in the second study, there were 5 SNPs that remained independent predictors; and after verification in the third study, only rs3798220 remained as the SNP most strongly associated with severe CAD. The adjusted OR for rs3798220 was 3.14 (95% CI: 1.51-6.56).

- In a similar case-control design, Shiffman et al.[8] examined the association between the rs3798220 allele and MI in 3 case-control studies totaling 762 cases and 857 controls. Starting from a total of 1,949 SNPs associated with MI, the authors identified 5 SNPs that were mostly strongly associated with MI. One of these was rs3798220, which had ORs in the 3 separate study populations of 1.59 (95% CI: 1.03-2.48), 1.72 (95% CI: 1.19-2.49), and 3.52 (95% CI: 1.85-6.69).

- The risk associated with genetic variants of LPA in diabetic patients may be different from that in the general population. A large prospective study performed in 2011 evaluated 2,308 patients with diabetes for LPA variants.[9] There was no significant association between genetic variants and cardiovascular risk or mortality. Odds ratios for coronary heart disease, cardiovascular disease, and cardiovascular death were 0.94 (95% CI: 0.69-1.28), 0.97 (95% CI: 0.72-1.29), and 1.23 (95% CI: 0.79-1.92), respectively. The authors also examined the degree of variability in risk between the diabetic and non-diabetic populations and reported that there was significant heterogeneity between the 2 groups (p=0.006).

- A case-control study of 2,136 cases and 1,211 controls evaluated if SNPs rs3798220 and rs10455872 were associated with an increased risk of coronary disease.[10] Genotyping of these SNPs and 7 other LPA variants believed to be associated with coronary disease was done by Taqman assay. After adjusting for conventional risk factors, the authors found an increased odds of MI of 2.14 (95% CI: 1.37-3.33, p=0.00080) and 1.45 (95% CI: 1.36-2.24, p <0.00001) for rs3798220 and rs10455872 respectively. Two additional SNPs, rs3127599 and rs9346818, were also found to be associated with risk of MI, with odds ratios of 1.18 (95% CI: 1.06-1.32) and 0.88 (95% CI: 0.79-0.97) respectively.

- A Danish cohort study of 8,720 participants was followed for 10 years to determine if LPA variants or lipoprotein(a) levels increased the risk of a first-time MI or CHD event.[11] Genotyping of rs3798220, rs10455872 and LPA-KIV-2 repeat genotype was performed by PCR. The authors found that 21% of the total variation in lipoprotein(a) levels was explained by the LPA-KIV-2, that 5% of the variation was explained by rs3798220 genotype, and that 27% of the variation was explained by rs10455872 genotype. The hazard ratio for carriers of rs3798220 was 1.3 (95% CI: 0.8-2.1) for MI and 1.4 (95% CI: 1.1-1.9) for CHD compared to noncarriers. LPA rs10455872 carriers had hazard ratios of 1.3 (95% CI: 1.1-1.6) for MI and 1.1 (95% CI: 0.9-1.3) for CHD compared to noncarriers, whereas homozygous rs10455872 patients had hazard ratios of 1.2 (95% CI: 0.5-3.3) for MI and 1.1 (95% CI: 0.5-2.1) for CHD compared to noncarriers.

Conclusion

Evidence from the above studies is sufficient to conclude that the genetic variant rs3798220 is an independent risk factor for cardiovascular disease. However, it has not been determined whether measurement of the genetic variant is superior to measurement of LPA levels as an independent risk factor for cardiovascular disease.

Patient Management and Improved Patient Outcomes

Will identification of the rs3798220 variant lead to changes in management, and will these changes in management lead to improved patient outcomes?

- The Women's Health Study (WHS) examined the efficacy of aspirin treatment versus placebo for primary prevention of cardiovascular events in healthy women. Chasman et al.[12] published a post hoc analysis of 28,345 participants in the WHS who were genotyped for the presence of the LPA rs3798220 minor allele. The allele was present in 3.7% of the population, 3.6% who were heterozygotes and 0.06% who were homozygotes. As expected, LPA levels in carriers of the allele were markedly elevated compared to non-carriers, and carriers had a 2-fold increased risk for subsequent cardiovascular events compared to non-carriers.

  The authors reported an interaction between the presence of the LPA rs378220 allele and response to aspirin therapy. In carriers there was a significant risk reduction associated with aspirin (ASA) treatment, with cardiovascular events occurring in 4.8% of patients in the placebo group compared to 2.1% in the aspirin group (HR: 0.44, 95% CI: 0.20-0.94, p=0.03). For non-carriers of the allele, there was no significant reduction in cardiovascular events associated with aspirin treatment, with cardiovascular events occurring in 2.3% of the placebo group compared to 2.1% of the aspirin group (HR: 0.91, 95% CI: 0.77-1.08, p=0.30).

- Shiffman et al.[13] reported data on the interaction of the LPA rs3798220 variant and aspirin use from the Atherosclerosis Risk in Communities (ARIC) study. The ARIC study was a prospective cohort study of risk factors for CAD in 15,792 individuals. The LPA genetic substudy of ARIC included 6,752 individuals with data available for LPA genotype and ASA use, including 221 individuals with the LPA rs3798220 genotype. Among carriers of rs3798220, the risk of cardiovascular events was compared in aspirin users and non-users. The hazard ratio for non-aspirin users (n=168) was elevated at 1.57 but did not reach statistical significance (95% CI: 0.92-2.69), while the HR for users of aspirin was not elevated at 0.86 (95% CI: 0.38-1.95).

Conclusion

These data are supportive, but not conclusive, of the hypothesis that carriers of the rs3798220 allele may derive greater benefit from aspirin therapy compared to non-carriers. It is not clear how this information would be used in clinical care. For patients who are currently recommended to receive aspirin, a negative genetic test is probably not sufficient to warrant withholding aspirin. Similarly, for patients who are not currently recommended to receive aspirin, a positive genetic test is probably not sufficient to warrant starting aspirin. Additionally, it is unclear whether rs3798220 testing holds any additional prognostic value over LPA level testing. Therefore, it remains to be determined whether results of rs3798220 testing leads to changes in management and whether these changes in management improve outcomes.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified that recommend rs3798220 gene testing.[14,15]

Summary

The Lipoprotein(a) (LPA) minor allele rs3798220 is associated with higher levels of LPA and a higher

risk for cardiovascular events; however, genetic testing performance characteristics are uncertain and standardization of testing has not been demonstrated. In addition, the current evidence is insufficient to determine whether information derived from genetic testing leads to changes in clinical management. In particular, it cannot be determined from the available evidence whether deviating from current aspirin therapy treatment guidelines based on Lipoprotein(a) (LPA) genetic testing improves outcomes. Therefore, measurement of the LPA rs3798220 variant as a decision aid for aspirin treatment is considered investigational.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81479	Unlisted molecular pathology procedure
	84999	Unlisted chemistry procedure
HCPCS	None	