Near-Continuous Association Between Lipoprotein(a) Level and CHD Risk Independent of Established Cardiovascular Risk Factors

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 2008;168:598–608.

Study Overview

Objective. To examine the stability of lipoprotein(a) levels over time and to assess whether the risk of coronary heart disease (CHD) increases in a linear fashion with rising lipoprotein(a) levels.

Design. Prospective, population-based, nested case-control study.

Setting and participants. 18,569 individuals with no history of myocardial infarction (MI) living in Reykjavik, Iceland, were recruited in 5 stages between 1967 and 1991 and chose to participate [1]. Baseline fasting venous blood samples were collected from all patients, and lipoprotein(a) levels were measured by enzyme-linked immunosorbent assay. Patients were monitored for the occurrence of major cardiovascular morbidity or cause-specific mortality. 2459 patients experienced either a first-ever nonfatal MI or coronary death; of these patients, 2047 as well as 3921 matched control patients were included in this analysis. Paired measurements were obtained from 372 participants approximately 12 years apart.

Main outcome measures. Odds of developing CHD in relation to lipoprotein(a) level, correlation of lipoprotein(a) levels with known cardiovascular risk factors, and lipoprotein(a) levels over time.

Main results. For the 372 participants who provided paired samples over 12 years, the lipoprotein(a) levels were extremely consistent over time. Higher levels of lipoprotein(a) were consistently associated with a higher odds ratio (OR) for CHD. After adjusting for other cardiovascular risk factors (ie, age, sex, smoking status, blood pressure, total cholesterol, triglyceride level, diabetes, body mass index), patients in the top quintile of lipoprotein(a) had a substantially higher risk of developing CHD as compared with patients in the lowest quintile of lipoprotein(a) (OR, 1.77 [95% confidence interval, 1.57–1.99]; $P < 0.001$). The higher risk was present among both men and women. Lipoprotein(a) levels were weakly associated with other cardiovascular risk factors (eg, hypertension, cholesterol).

Conclusion. Serum lipoprotein(a) levels may serve as accurate predictors of future CHD. Lipoprotein(a) is independent of other known cardiovascular risk factors and levels remain constant over time and demonstrate similar positive predictive values for various patient subgroups.

Commentary

Given the high morbidity and mortality associated with CHD, identifying additional cardiovascular risk factors is a high priority for clinicians. Several studies have shown that lipoprotein(a) is associated with an increased risk of cardiovascular disease [2]; however, the strength of this association has been variable and some studies have failed to find any relationship at all. Most prior studies have been underpowered to determine the exact relationship between lipoprotein(a) and CHD (eg, whether the relationship is linear, whether there is a threshold effect). Further, prior studies have not adequately examined subgroups to determine whether the risks are comparable for both men and women.

Using data from a large cohort of men and women living in Iceland, Bennet and colleagues determined that lipoprotein(a) levels are stable over time, that these levels are linearly related with CHD risk, and that the risks are comparable for men and women. Further, although patients with elevated lipoprotein(a) levels also had higher rates of other cardiovascular risk factors, the risk associated with lipoprotein(a) seemed to be independent of other known contributors to CHD, such as hypertension and cholesterol.

Although this study firmly establishes lipoprotein(a) as a marker for patients at higher risk for CHD, it does not yet provide a clear path for clinicians to follow. The authors imply, but hardly prove, that lowering lipoprotein(a) levels might reduce the incidence of CHD. However, it is unclear from this study (or other studies) whether lipoprotein(a) is a direct cause of CHD or a marker of some other, yet unknown contributing factor. This distinction is critical to understanding whether clinicians should be targeting therapies to lower

lipoprotein(a) levels. Further, given that the study included a homogenous group of white individuals living in Iceland, it is unclear how these findings relate to other racial and ethnic groups.

Applications for Clinical Practice

The study by Bennet et al provides convincing evidence that lipoprotein(a) levels are stable over time and an important marker of elevated CHD risk. Because lipoprotein(a) is stable over time, a 1-time test could identify a cohort of patients who might benefit from aggressive risk factor management for other known contributors to CHD (eg, hypertension, smoking). Currently, there is no evidence that monitoring or lowering lipoprotein(a) levels is clinically useful.

—Review by Ashish K. Jha, MD, MPH

References

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2. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. Circulation 2000;102:1082–5.