(2), we found Lp(a) concentrations to be by far the best predictor of the *extent* of coronary disease, as measured by an angiographic stenosis score (Table 1) in both white and Indo-Asian patients. Again, this finding accords with previous reports. Are the data really so contradictory?

As we pointed out some years ago (3), although the individual risk of myocardial infarction correlates with coronary disease burden, on a population basis, the commonest angiographic finding in whites presenting <70 years old with a first myocardial infarction is single-vessel disease. It is therefore not surprising that Lp(a) concentration is a mediocre predictor of myocardial infarction risk in Australian whites, although as Kinlay et al. acknowledge, a different pattern may emerge in blacks or Indo-Asians, who are more likely to have multivessel disease at the time of a first infarction. Interpretation of recurrent infarction risk is more difficult, particularly because multivessel disease will adversely influence survival. I accept the fact that measuring Lp(a) concentrations to predict infarction risk is unprofitable, but let us not discard Lp(a) as a major factor just yet. The real message is that studies using different end points will often give different answers, and reconciling these may enhance our understanding of atherosclerosis as a whole.

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References

1. Kinlay S, Dobson AJ, Heller RF, McElduff P, Alexander H, Dickeson S. Risk of primary and recurrent acute myocardial infarction from lipoprotein(a) in men and women. J Am Coll Cardiol 1996;28:870–5.
2. Shaukat N, de Bono DP, Jones D. Like father like son? Sons of patients of European or Indian origin with coronary heart disease reflect their parents' risk factor patterns. Br Heart J 1995;74:318–23.
3. de Bono DP, Bhattacharrya AK. Segmental analysis of coronary arterial stenoses in patients with angina or first myocardial infarction. Int J Cardiol 1991;32:313–22.

Reply

Establishing cause and effect is a scientific goal that helps to advance our understanding of disease and offer insights into the prevention of disease. Although an association between a potential risk factor and disease can support a causal link, it is not sufficient evidence to prove cause and effect. As Bradford-Hill summarized several decades ago (1), establishing cause and effect requires numerous pieces of evidence that include a strong association between the factor and disease, a consistent association across several studies, a proper temporal relationship (the risk factor occurs before the disease) and a biologically plausible mechanism.

Unlike total cholesterol and low and high density lipoprotein cholesterol, lipoprotein(a) [Lp(a)] concentrations satisfy few of these requirements as a causal factor for coronary heart disease (CHD). Although there is a very plausible biological mechanism [apolipoprotein(a) homology to plasminogen and the potential to interfere with fibrinolysis], the epidemiologic evidence is notably inconsistent.

Much of the support for Lp(a) as a CHD risk factor comes from cross-sectional studies of referred populations, such as those from cardiac catheterization laboratories (2–7), lipid clinics (8) or selected populations (9). Cross-sectional studies cannot examine the temporal relationship of Lp(a) to CHD, and referred populations that are selected by the presence of disease or known risk factors can result in biased interpretations. Even the cross-sectional studies of Lp(a) in children and disease in adults, such as those referred to by Enas (9,10), do not account for the possibility that early manifestations of vascular disease, such as endothelial dysfunction, may influence Lp(a) levels in children (11).

The cross-sectional angiographic study of Shaukat et al. (7) found a correlation between Lp(a) and an ad-hoc scoring system of extent of coronary disease (6). However, the substantial correlations between Lp(a) and some of the other metabolic variables in their study (7) makes the interpretation of their multivariate models difficult. The univariate analyses in their study suggested that insulin levels and total cholesterol were more strongly related to extent of disease than Lp(a) (7).

There are undoubtedly genetic differences in apolipoprotein(a) frequencies that have a strong influence on the differences in Lp(a) between some racial groups. However, cross-sectional studies between populations or different races within the same population cannot determine whether Lp(a) causes CHD, is a consequence of vascular disease or is related to CHD indirectly by confounding factors that increase both Lp(a) concentrations and CHD risk.

Enas' concern that patients who died before reaching the hospital in our study may have biased our results is not supported by either of the studies he cites (12,13). These studies followed up survivors of myocardial infarction and would have missed at least as many patients who died before enrollment. The first study (12) examined prognosis related to blood samples collected 3 months after myocardial infarction and excluded one-third of the sample from the multivariate analysis. The second study (13) found a weak and marginally statistically significant association with Lp(a) and recurrent myocardial infarction on univariate analysis ($p = 0.05$). On multivariate analysis, Lp(a) >30 mg/dl was associated with an odds ratio of 2.16 for further acute ischemic events ($p = 0.037$) (11).

The prospective population studies, and prospective angiographic studies (14), are also divided as to whether Lp(a) was or was not associated with CHD. Although some studies found statistically significant results, the relative risks for the highest levels of Lp(a) are not large, with most odds ratios/relative risks <2.0 to 2.5.

The inconsistency and generally weak magnitude of risk in the epidemiologic data cast strong doubts on the case for Lp(a) as a CHD risk factor. We propose that Lp(a) could be a marker of vascular or tissue damage (14) and that this damage may contribute to serum levels, along with the well recognized genetic component. Our hypothesis may be incorrect, but until interventions are demonstrated to be of greater value in patients with elevated Lp(a) concentrations, there is no clinical justification for measuring Lp(a).

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References

1. Bradford-Hill A, Hill ID. Bradford-Hill's Principles of Medical Statistics. 12th ed. London: Edward Arnold, 1991.
2. Dahlen GH, Guyton JR, Altar M, Farmer JA, Kautz JA, Gotto AM. Association of levels of lipoprotein(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. Circulation 1986;74:758–65.
3. Genest J Jr, Jenner JL, McNamara JR, et al. Prevalence of lipoprotein(a) [Lp(a)] excess in coronary artery disease. Am J Cardiol 1991;67:1039–45.
4. Wang XL, Tam C, McCredie RM, Wilcken DEL. Determinants of severity of coronary artery disease in Australian men and women. Circulation 1994;89:1974–81.
5. Parlavecchia M, Pancaldi A, Taramelli R, et al. Evidence that apolipoprotein(a) phenotype is a risk factor for coronary artery disease in men <55 years of age. Am J Cardiol 1994;74:346–51.
6. de Bono D. Risk of primary and recurrent acute myocardial infarction from lipoprotein(a)—II [letter]. J Am Coll Cardiol 1997;29:887.
7. Shaukat N, de Bono DP, Jones DR. Like father like son? Sons of patients of European or Indian origin with coronary artery disease reflect their parents' risk factor patterns. Br Heart J 1995;74:318–23.
8. Seed M, Hoppichler F, Reaveley D, et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. N Engl J Med 1990;322:1494–9.
9. Wilcken DEL, Wang XL, Greenwood J, et al. Lipoprotein(a) and apolipoprotein B and A-1 in children and coronary vascular events in grandparents. J Pediatr 1993;123:519–26.
10. Hoeffler G, Harnoncourt F, Paschke E, et al. Lipoprotein Lp(a)—a risk factor for myocardial infarction. Arteriosclerosis 1988;8:398–401.
11. Sorensen KE, Celermajer DS, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE. Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. J Clin Invest 1994;93:50–5.
12. Hamsten A, Walldius G, Szamosi A, et al. Plasminogen activator inhibitor in plasma; risk factor for recurrent myocardial infarction. Lancet 1987;2:3–9.
13. Stubos P, Collinson P, Kenadall F, et al. The prognostic significance of lipoprotein concentrations following myocardial infarction [abstract]. Heart 1996;75 Suppl 1:77.
14. Kinlay S, Dobson AJ, Heller RF, McElduff P, Alexander H, Dickeson J. Risk of primary and recurrent acute myocardial infarction from lipoprotein(a) in men and women. J Am Coll Cardiol 1996;28:870–5.