Risk of Primary and Recurrent Acute Myocardial Infarction From Lipoprotein(a)—I

Numerous studies in newborns, infants, children, adults, parents and grandparents have conclusively demonstrated that serum levels of lipoprotein(a) [Lp(a)] are largely genetically determined, with full expression of the Lp(a) gene in the first year of life. Serum levels of Lp(a) increase twofold between the first week and 8.5 months of age to reach stable, life-long levels (1). Lp(a) levels at 8.5 months of age are not different from parental values and are closely correlated with that of the affected parent (1). Lp(a) levels in children 8 to 12 years old are highly correlated with premature coronary artery disease (CAD) and "coronary history score" in grandparents (2). Parents of male children with Lp(a) levels >25 mg/dl have a 2.5-fold higher incidence of myocardial infarction (MI) (3). I therefore disagree with the conclusion of Kinley et al. (4) from the Australian Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study that elevated serum levels of Lp(a) may be the effect of advanced atherosclerosis and MI rather than the cause. The results from two other MONICA centers appear to provide insights into the paradoxically higher Lp(a) levels in patients without than with recurrent MI. In the Scottish MONICA study (5), compared with age-matched men, the fatality rates for MI in women were 14% higher after admission to the hospital and 22% higher after admission to coronary care, yet the case fatality rates at 28 days were identical (men 49.8%; women 49.6%). Women had more shock and syncope and had a worse prognosis in the hospital only because an equivalent number of men had died suddenly before reaching the hospital. Prehospital death accounted for 74% of deaths in men compared with only 65% in women (5). The New Zealand MONICA study (6) also had similar results, with identical 28-day case fatality rates in both men and women. The higher case fatality rate after hospital admission was compensated by a lower prehospital CAD case fatality in women. A higher rate of death after MI in patients with high levels of Lp(a) is highly plausible, as discussed later.

In a study (7) of 79 Swedish men who survived an MI before the age of 45, reinfarction occurred within 3 years in 16 and was fatal in 9 (56%). Lp(a) levels were highly correlated with the coronary stenosis score as well as the recurrence of MI. Mean Lp(a) levels were twofold higher in patients without and fourfold higher in those with recurrent MI than in the control population. In a British study of 266 patients followed up for 965 days after an acute MI, elevated levels of Lp(a) were an independent risk factor for cardiac mortality, with a relative risk of 2.16 on multivariant analysis (8). Those patients with Lp(a) levels >30 mg/dl had a significantly higher cardiac mortality rate (29.8% vs. 18.6%, p = 0.05) than those with Lp(a) levels <30 mg/dl.

Patients with higher levels of Lp(a) in the present study (4) indeed had advanced coronary atherosclerosis disease, a powerful prognostic factor for cardiac morbidity and mortality, including out of hospital deaths (9). Others (10,11) have also reported significant correlation of Lp(a) levels with the extent, severity and rapid angiographic progression of CAD (12), all of which are highly predictive of the development of clinical coronary events and mortality after an MI (13). Thus, the exclusion of patients who died outside the hospital in the study by Kinley et al. (4) may have biased their results and conclusions.

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Risk of Primary and Recurrent Acute Myocardial Infarction From Lipoprotein(a)—II

Kinlay et al. (1) have shown, as have others, that a high lipoprotein(a) [Lp(a)] concentration is a significant but weak predictor of myocardial infarction risk. In contrast, in a recent prospective cross-sectional study

Table 1. Independent Predictors ($p < 0.01$) of Coronary Artery Disease Score in White or Indo-Asian Patients Ranked in Order of Explanatory Value (contribution to cumulative adjusted r^2)*

Metabolic Variable	Cumulative r^2 Value
White patients (n = 102)	
Lp(a)	0.24
Fasting insulin	0.38
Total cholesterol	0.45
Triglycerides	0.50
Indo-Asian patients (n = 102)	
Lp(a)	0.21
Total cholesterol	0.35
Fasting insulin	0.41
HDL cholesterol	0.45

*Data from Shaukat et al. (2). HDL = high density lipoprotein; Lp(a) = lipoprotein(a).

(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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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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