Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease

Paul J. Nestel, Elizabeth H. Barnes, Andrew M. Tonkin, John Simes, Marion Fournier, Harvey D. White, David M. Colquhoun, Stefan Blankenberg, David R. Sullivan

Objective—Association between lipoprotein(a) (Lp(a)) level and a first-ever coronary (CHD) event is recognized. Less is evident in patients with overt CHD and stable symptoms in whom we investigated associations between Lp(a) and future events.

Approach and Results—Relationships between Lp(a) concentration and CHD and cardiovascular disease outcomes during 6 years’ median follow-up were evaluated in the Long-Term Intervention with Pravastatin In Ischaemic Disease (LIPID) study. Lp(a) concentrations were measured in plasma from 7863 patients who had sustained a previous coronary event and been randomized to pravastatin or placebo. Lp(a) levels were categorized by lowest half, third quartile, 75th to 90th percentile, and highest decile. The prognostic value of Lp(a) on outcomes was assessed by fitting a Cox proportional-hazards model after adjustment for other risk factors and baseline cardiovascular disorders. The prognostic value of a change in Lp(a) at year 1 categorized by quartiles was assessed using Cox regression in a landmark model incorporating the above factors and baseline levels. Baseline Lp(a) concentration was associated with total CHD events (P<0.001), total cardiovascular disease events (P=0.002), and coronary events (P=0.03). Greatest risk occurred at >73 mg/dL, upper decile. For events after year 1, an increase in Lp(a) at 1 year was associated with adverse outcomes for total CHD events and total cardiovascular disease events (P=0.002 each).

Conclusions—In the LIPID study, baseline Lp(a) was associated with future cardiovascular disease and CHD events. Increased Lp(a) concentrations after 1 year were also associated with future events, supporting measurement of Lp(a) for risk assessment of patients with known CHD. (Arterioscler Thromb Vasc Biol. 2013;33:2902-2908.)

Key Words: cardiovascular diseases ■ coronary disease ■ lipoprotein(a) ■ pravastatin

Lipoprotein(a) (Lp(a)) is a recognized risk factor for coronary heart disease (CHD). Population studies and meta-analyses show association between Lp(a) levels and first-ever CHD events, but there is less evidence in patients with overt CHD and stable clinical symptoms. In a general population cohort (Copenhagen City Heart Study), the hazard ratio (HR) for future CHD reached a significant value of 1.9 between the 67th and 89th percentiles of Lp(a) concentration. Furthermore, as reported by Kamstrup et al, risk rises most in those patients whose Lp(a) concentration is in the top decile. Causality was predicated on the basis of a strong genetic influence on the Lp(a) level through the kringle IV type 2 size polymorphism which had been shown also to associate with future myocardial infarction. In a meta-analysis of 36 prospective studies that yielded 9318 cases of nonfatal myocardial infarctions and CHD deaths, the risk ratio became significant above Lp(a) levels of ≈50 mg/dL. For the 22,076 first-ever fatal or nonfatal cardiovascular disease (CVD) outcomes, the association with Lp(a) was broadly continuous but modest. These findings were consistent with preceding reports based on fewer studies that showed an average 1.7-fold increased risk for ischemic heart disease between the upper and lower thirds of the Lp(a) distribution. A recent very large 20-year prospective cohort study of 3467 blacks and 9851 whites showed a graded risk between Lp(a) concentration and incident CVD events which was significant only when the highest and lowest quintiles were compared with respective HRs of 1.35 and 1.27 for the 2 populations. The importance of Lp(a) size polymorphisms had been appreciated for some time and summarized in a review of 36 studies that showed a doubling in CHD risk in the presence of the smaller rather than the larger isoforms (risk ratio of 2.08 for the smaller isoforms). By contrast, isoform size was not a predictor of future CHD events in a 12.3-year prospective study of the Framingham Offspring Cohort, although elevated Lp(a) levels were found to have independent significant associations with CHD in men but not in women.
argument for inclusion of Lp(a) concentration within a global risk profile assessment was further supported by the findings in the Prospective Cardiovascular München prospective cohort study in which Lp(a) levels $>20$ mg/dL were associated with a 2.7-fold greater risk of CHD events compared with lower levels, although this was predominantly in men who also suffered from other forms of dyslipidemia and hypertension.\textsuperscript{10} Lp(a) concentrations also associate significantly with the severity of coronary atherosclerosis. In a coronary angiographic study among 2769 patients being treated with statins, elevated Lp(a) defined as $>30$ mg/dL was associated with a 2.3-fold greater likelihood of significant stenosis and a 1.5-fold greater rate of major CVD events, particularly revascularizations.\textsuperscript{11} A consensus paper issued by the European Atherosclerosis Society in 2010\textsuperscript{12} describes Lp(a) as a causal risk factor for CHD and CVD, recommending screening for Lp(a) in people judged to be at intermediate or high risk for future CVD/CHD and treating to levels $<50$ mg/dL.

Thus, Lp(a) appears to be an independent risk factor in both primary and secondary settings, although much of the evidence derives from cohorts who were initially apparently free of overt CVD. There is a paucity of information on the predictive value of Lp(a) in patients with stable CVD. We report here the relationships between Lp(a) concentrations and further CHD and CVD events in patients who entered a trial of statin therapy after suffering a myocardial infarction or an admission with unstable angina, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.\textsuperscript{13}

### Materials and Methods

Materials and Methods are available in the online-only Supplement.

### Results

Table 1 shows the characteristics of the 7863 patients by categories of Lp(a) at baseline. The median concentration of Lp(a) at baseline was 13.9 (25th–75th percentiles, 6.6–44.05) mg/dL with the upper decile $>73.7$ mg/dL; none had values $>90$ mg/dL. Half the patients had values $<13.9$ mg/dL, which are considered normal. Baseline risk factors by Lp(a) categories demonstrate significant differences according to Lp(a). The proportion of obese and diabetic subjects diminished at higher levels as did the median plasma triglyceride concentration ($P<0.001$ for all), total and low-density lipoprotein cholesterol levels were both higher, but Lp(a) itself would have contributed to the cholesterol content of low-density lipoprotein cholesterol.\textsuperscript{3} Patients whose qualifying event for the study was not a previous myocardial infarction but hospitalization for unstable angina were distributed significantly more frequently in the higher Lp(a) levels as were patients with a computed lower total risk score, the components of which we have published previously.\textsuperscript{14}

Table 2 shows that Lp(a) concentrations did not differ between patients allocated placebo or pravastatin either at baseline or at 1 year (13.4 and 14.3 mg/dL; $P=0.11$ and 12.9 and 13.4 mg/dL; $P=0.40$ for placebo and pravastatin groups, respectively). On average, Lp(a) concentrations did not change significantly at 1 year with an overall median change of $-0.3$ (interquartile range from $-2.4$ to 1.0) mg/dL.

The possible prognostic values of baseline Lp(a) levels and of the changes in Lp(a) from baseline to 1 year are shown in Tables 3 and 4, respectively. Baseline Lp(a) concentrations have been analyzed to include the following: (1) the lowest 2 quartiles combined; (2) the third quartile; (3) the 75th to 90th percentiles; and (4) the upper decile. Lp(a) concentration at baseline was weakly associated with the prespecified primary outcome of CHD death or nonfatal myocardial infarction (Table 3; $P=0.03$). It was not associated with nonhemorragic stroke (data not shown). However, several prespecified secondary outcomes including total CHD events ($P=0.001$), total CVD events ($P=0.002$), and coronary revascularization ($P<0.001$) were significantly associated with baseline Lp(a) concentrations (Table 3).

The change in Lp(a) concentration to 1 year was of highly significant prognostic value in the Landmark model ($P=0.002$ for both future total CHD and total CVD outcomes; Table 4), although the association with stroke alone was not significant. This effect resulted in patients in the top quartile of change (whose Lp(a) increased by $\geq 3.4$ mg/dL) experiencing total CVD events at a 23% higher rate than those in the lowest quartile (whose Lp(a) decreased by $\geq 2.4$ mg/dL; HR, 1.23; 95% confidence interval, 1.07–1.39; $P=0.002$). For total CHD events, the effects were similar (HR, 1.22; 95% confidence interval, 1.08–0.41; $P<0.0001$). An increase in Lp(a) from baseline to year 1 was also associated with a modest increase in the HR for CVD death (HR, 1.33; 95% confidence interval, 1.02–1.74; $P=0.04$).

Two issues that may have modified the results relating to change in Lp(a) concentration during the first year were analytic variation in the 2 measurements and the possible effect of change in low-density lipoprotein cholesterol. The methodology to address those issues has been described under Materials and Methods in the online-only Data Supplement. The data shown in landmark analysis (Table 4) have been reanalyzed accounting for both issues. A relative change $>13\%$ from baseline is larger than can be accounted for by analytic variation. Adjusting for both issues, the levels of significance for the 2 key secondary outcomes were attenuated only marginally. For total CVD events, across the categories, decrease by $>13\%$, remaining within 13% of the baseline, and increasing by $>13\%$, the HR for those showing $>13\%$ increase was 1.21 (1.06–1.39; $P=0.005$) relative to those whose Lp(a) decreased by $>13\%$ below their baseline level. For total CHD events, the corresponding HR was 1.21 (1.05–1.39; $P=0.009$).

Whether the above findings might have added to the predictive value of Lp(a) concentration on future cardiovascular events was examined by C statistic analysis and classification-free net reclassification index. The C statistic was unaltered by the addition of Lp(a), but net reclassification index ranged from 2% to 11% for the outcomes listed in Table 1.

### Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>LIPID</td>
<td>Long-Term Intervention with Pravastatin in Ischaemic Disease</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>lipoprotein(a)</td>
</tr>
</tbody>
</table>
Pravastatin treatment remained highly significant in its effect on the prespecified outcomes (P<0.03; Tables 3 and 4), and there was no interaction between baseline Lp(a) and pravastatin treatment in their effects on cardiovascular outcomes. Similarly, there was no significant interaction between Lp(a) level and sex on outcomes.

Lp(a) concentration did not correlate with any of the parameters including apolipoprotein B at baseline, but change in Lp(a) correlated weakly with changes in hsC-reactive protein (r=0.09) and somewhat more strongly with changes in high-density lipoprotein cholesterol (r=0.09), low-density lipoprotein cholesterol (r=0.23), total cholesterol (r=0.14), triglycerides (r=−0.17), and apolipoprotein B (r=0.15) but not with creatinine or estimated glomerular filtration rate (r=0.00 for both), but all correlations were weak.

### Discussion

In contrast to the relatively consistent predictive strength of baseline Lp(a) concentration on future cardiovascular events in subjects without overt CHD, our findings in subjects with stable CHD also demonstrate a significant effect on a composite of multiple cardiovascular outcomes. Several meta-analyses...
of large numbers of prospective and case–control studies do include both primary and secondary outcome studies, although the former predominate.2–5 Our study, therefore, supports the likelihood that Lp(a) represents a significant risk factor for recurrent events. Furthermore, the findings were attributable particularly to effects in those with substantially higher Lp(a) values, namely the highest decile (>73 mg/dL). This is consistent with recent suggestions that an Lp(a) level of >50 mg/dL should be considered a robust cutoff value at which the risk for CVD events particularly increases.12 On the contrary, a recent study demonstrated a graded response extending into lower concentrations of Lp(a).7 Other large prospective studies, such as the recently reported Women’s Health Study, suggest a nongraded association with clear adverse cardiovascular outcomes becoming evident in the highest quintile.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Variable</th>
<th>Baseline Lp(a) Concentration, mg/dL</th>
<th>Events, n/Total</th>
<th>5-Year Event Rate, %</th>
<th>HR (95% CI)*</th>
<th>P Value (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events*</td>
<td>Lp(a)</td>
<td>≤13.9</td>
<td>544/3949</td>
<td>11.5</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9–44.1</td>
<td>260/1938</td>
<td>11.2</td>
<td>0.96 (0.83–1.12)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.1–73.7</td>
<td>172/1187</td>
<td>12.3</td>
<td>1.07 (0.90–1.27)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>124/789</td>
<td>13.1</td>
<td>1.24 (1.02–1.52)</td>
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<tr>
<td></td>
<td>Pravastatin</td>
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<td>…</td>
<td>…</td>
<td>0.80 (0.71–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>Lp(a)</td>
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<td>6.4</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9–44.1</td>
<td>150/1938</td>
<td>6.7</td>
<td>1.06 (0.87–1.30)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.1–73.7</td>
<td>110/1187</td>
<td>8.2</td>
<td>1.28 (1.02–1.60)</td>
<td>…</td>
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<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>68/789</td>
<td>7.6</td>
<td>1.30 (0.99–1.70)</td>
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<tr>
<td></td>
<td>Pravastatin</td>
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<td>…</td>
<td>…</td>
<td>0.80 (0.68–0.94)</td>
<td>0.006</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Lp(a)</td>
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<td>911/3949</td>
<td>20.8</td>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
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<td>13.9–44.1</td>
<td>410/1938</td>
<td>19.2</td>
<td>0.90 (0.80–1.02)</td>
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<td></td>
<td></td>
<td>44.1–73.7</td>
<td>303/1187</td>
<td>22.6</td>
<td>1.07 (0.94–1.22)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>205/789</td>
<td>24.9</td>
<td>1.14 (0.98–1.34)</td>
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</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.88 (0.80–0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>Lp(a)</td>
<td>≤13.9</td>
<td>546/3949</td>
<td>12.4</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9–44.1</td>
<td>269/1938</td>
<td>12.2</td>
<td>1.04 (0.90–1.21)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>44.1–73.7</td>
<td>179/1187</td>
<td>13.1</td>
<td>1.09 (0.91–1.29)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>145/789</td>
<td>16.8</td>
<td>1.45 (1.20–1.75)</td>
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</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.83 (0.74–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total CVD events†</td>
<td>Lp(a)</td>
<td>≤13.9</td>
<td>1508/3949</td>
<td>33.5</td>
<td>1</td>
<td>0.002</td>
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<td></td>
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<td>13.9–44.1</td>
<td>712/1938</td>
<td>32.3</td>
<td>0.95 (0.87–1.04)</td>
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<td></td>
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<td>44.1–73.7</td>
<td>481/1187</td>
<td>34.3</td>
<td>1.06 (0.96–1.18)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>339/789</td>
<td>38.4</td>
<td>1.21 (1.07–1.36)</td>
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</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.84 (0.78–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CHD events‡</td>
<td>Lp(a)</td>
<td>≤13.9</td>
<td>1416/3949</td>
<td>31.5</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9–44.1</td>
<td>653/1938</td>
<td>29.9</td>
<td>0.93 (0.85–1.02)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.1–73.7</td>
<td>454/1187</td>
<td>32.7</td>
<td>1.06 (0.96–1.18)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;73.7</td>
<td>324/789</td>
<td>36.9</td>
<td>1.23 (1.09–1.40)</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.85 (0.79–0.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HRs and 95% CIs are adjusted for baseline variables: treatment, sex, stroke, diabetes mellitus, smoking, hypertension, total cholesterol, apolipoprotein B, apolipoprotein A1, HDL-c, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin use at baseline. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

*CHD events comprise nonfatal MI and CHD death.
†Total CVD events comprise CVD death, nonfatal MI, nonhemorrhagic stroke, unstable angina, and coronary revascularization.
‡Total CHD events comprise major CHD events, unstable angina, and coronary revascularization.

Table 2. Baseline, Year 1, and Change in Lp(a) by Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.4 (6.5 to 43.4)</td>
<td>14.3 (6.7 to 45.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Year 1</td>
<td>12.9 (6.1 to 41.4)</td>
<td>13.4 (6.1 to 43.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Change</td>
<td>−0.2 (−2.3 to 1.0)</td>
<td>−0.3 (−2.6 to 1.0)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Median (interquartile range) is presented. Lp(a) indicates lipoprotein(a).

*P values are from a Wilcoxon test.
of Lp(a) concentration (>44 mg/dL). However, the recently published meta-analysis by Di Angelantonio et al\textsuperscript{16} of 37 prospective cohort studies followed for a median of 10.4 years suggested that the Lp(a) concentration did not significantly improve net risk reclassification when added to conventional risk factors. In our study, the net reclassification index showed modest improvements in some CVD outcomes. Lp(a) levels also predict severity of coronary atherosclerosis in clinically symptomatic patients.\textsuperscript{11}

Both the baseline concentration of Lp(a) and the change in Lp(a) levels in the first year showed highly significant associations for events that occurred after the first year with 2 secondary end points, total CHD events and total CVD events (Tables 3 and 4). Furthermore, we did not observe important attenuation in the levels of significance for the effects of Lp(a) change after adjusting for possible confounding by analytic variation in Lp(a) measurements and for changes in low-density lipoprotein cholesterol. An effect of statin therapy can be largely excluded because pravastatin did not affect Lp(a) level (Table 2). The risk of the outcomes occurring was greater when Lp(a) levels increased >13\% and was lower when Lp(a) levels declined by >13\% during the first year. Although Lp(a) levels are regarded as fluctuating little over time at least on average, individual subjects may show either increments or decrements, and this study demonstrated that a rising Lp(a) level is associated with cardiovascular events.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Variable</th>
<th>Change in Lp(a) Concentration, mg/dL</th>
<th>Events, n/Total</th>
<th>4-Year Event Rate, %</th>
<th>HR (95% CI)*</th>
<th>P Value (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events*</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>185/1690</td>
<td>8.8</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.4 to −0.3</td>
<td>174/1624</td>
<td>9.0</td>
<td>0.99 (0.79–1.24)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>−0.3 to 1.0</td>
<td>162/1668</td>
<td>7.7</td>
<td>0.87 (0.70–1.10)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>193/1608</td>
<td>9.3</td>
<td>1.11 (0.90–1.36)</td>
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</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.76 (0.66–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>117/1690</td>
<td>6.0</td>
<td>1</td>
<td>0.77</td>
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<tr>
<td></td>
<td></td>
<td>−2.4 to −0.3</td>
<td>91/1624</td>
<td>4.9</td>
<td>0.88 (0.65–1.19)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>−0.3 to 1.0</td>
<td>81/1668</td>
<td>4.1</td>
<td>0.75 (0.55–1.03)</td>
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<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>114/1608</td>
<td>5.7</td>
<td>1.04 (0.80–1.36)</td>
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<tr>
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<td>Pravastatin</td>
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<td>...</td>
<td>...</td>
<td>0.80 (0.66–0.98)</td>
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<tr>
<td>Unstable angina</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>273/1603</td>
<td>15.3</td>
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<td>0.005</td>
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<td></td>
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<td>−2.4 to −0.3</td>
<td>271/1554</td>
<td>14.9</td>
<td>1.03 (0.85–1.24)</td>
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<td></td>
<td></td>
<td>−0.3 to 1.0</td>
<td>290/1591</td>
<td>15.3</td>
<td>1.08 (0.90–1.29)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>325/1547</td>
<td>18.3</td>
<td>1.27 (1.08–1.50)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.88 (0.78–0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Revascularization</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>182/1659</td>
<td>9.7</td>
<td>1</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.4 to −0.3</td>
<td>160/1598</td>
<td>8.9</td>
<td>1.04 (0.82–1.31)</td>
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<tr>
<td></td>
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<td>−0.3 to 1.0</td>
<td>199/1631</td>
<td>10.2</td>
<td>1.18 (0.95–1.47)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>178/1578</td>
<td>9.5</td>
<td>1.09 (0.88–1.35)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.74 (0.64–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CVD events†</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>453/1554</td>
<td>24.5</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.4 to −0.3</td>
<td>433/1508</td>
<td>24.9</td>
<td>1.00 (0.86–1.15)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.3 to 1.0</td>
<td>485/1541</td>
<td>25.5</td>
<td>1.08 (0.94–1.24)</td>
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<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>513/1491</td>
<td>28.5</td>
<td>1.22 (1.07–1.39)</td>
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</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.79 (0.72–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CHD events‡</td>
<td>Lp(a)</td>
<td>≤−2.4</td>
<td>417/1561</td>
<td>22.8</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2.4 to −0.3</td>
<td>410/1514</td>
<td>23.4</td>
<td>1.04 (0.89–1.21)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−0.3 to 1.0</td>
<td>445/1542</td>
<td>23.4</td>
<td>1.08 (0.93–1.25)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1.0</td>
<td>473/1493</td>
<td>26.4</td>
<td>1.23 (1.08–1.41)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.80 (0.73–0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HRs and 95\% CIs are adjusted for baseline Lp(a) and variables: treatment, sex, stroke, diabetes mellitus, smoking, hypertension, total cholesterol, apolipoprotein B, apolipoprotein A1, HDL-c, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin use at baseline. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

*CHD events comprise nonfatal MI and CHD death.
†Total CVD events comprise CVD death, nonfatal MI, nonhemorrhagic stroke, unstable angina, and coronary revascularization.
‡Total CHD events comprise major CHD events, unstable angina, and coronary revascularization.
Consequently, there was not a consistent picture favoring Lp(a) being associated with particular component outcomes. Rather it appears that Lp(a) (baseline and change) are moderately associated with a range of CVD outcomes with greater strength of association because more events are included.

Renal function did not deteriorate over this time. Change in Lp(a) correlated with change in lipids and lipoproteins, rather than creatinine or estimated glomerular filtration rate. The baseline Lp(a) concentration was inversely related to plasma triglyceride concentration and type 2 diabetes mellitus prevalence, as has been reported by others. This inverse association between Lp(a) concentration and type 2 diabetes mellitus (Table 1) appears paradoxical but confirms similar observations in the Women’s Health Study and the Copenhagen Heart Study.

The LIPID cohort is one of the best characterized trials in CHD with ascertainment of vital status in all but 1 patient and adjudication of major cardiovascular events, the end points in the present study, in all. The 7863 patients in whom adequate plasmas were stored under optimal conditions and available for a comprehensive biomarker investigation, including Lp(a), did not reflect loss to follow-up from the initial 9014-patient cohort. The reduced number reflected patients who had died or in whom samples of plasma were insufficient for the full range of assays.

Mechanisms that may account for the association of Lp(a) with CVD outcomes must be speculative in the absence of certainty about its functions. Potential antithrombotic activity has been proposed because of structural similarity with plasminogen the activity of which Lp(a) may oppose.

A recent editorial supported its role as a prothrombotic factor by pointing out that Lp(a) appears to be significantly associated with carotid artery occlusion but not plaque size. On the contrary, there may be a stronger linkage between the kringle IV type 2 genotype and atherosclerotic stenosis in large arteries than with thrombosis in veins. Further support for a stronger link to atherosclerosis than to thrombosis was reported from the Trial of Org 10172 in Acute Stroke, which investigated the association of 2 variants in the LPA gene with subtypes of acute stroke. LPA score from the 2 variants combined was significantly associated with large artery atherosclerosis ischemic stroke, peripheral artery disease, extent of coronary atherosclerosis, and abdominal aeurysm, but not with stroke caused by emboli or small vessel disease or with venous thrombosis. The 2 variants in the LPA gene have been shown to associate with higher Lp(a) concentrations, which in turn increase the risk of CVD. The consistent observations from the laboratory of Tsiminakis and Witzum of a strong correlation between the circulating levels of Lp(a) and oxidized phospholipid/apolipoprotein B complex which were together directly associated with CVD outcomes suggested to them that Lp(a) transported the proinflammatory burden of oxidized phospholipids. These findings that were attributed to possible increased efflux from plaques of the oxidized lipoprotein complex were demonstrated in prospective cohort studies and were associated with angiographic coronary artery disease. Elevated Lp(a) levels may augment the CHD risk from increased low-density lipoprotein cholesterol concentrations as has been demonstrated in patients with familial hypercholesterolemia. Experimental studies have shown that Lp(a) may contribute to foam cell formation. The possibility that Lp(a) may become functionally altered in patients with coronary artery disease has been put forward by Tsirionis et al on the basis of mass and specific activity of Lp(a) as mediator of platelet-activating factor acetylhydrolase activity, an enzyme that hydrolyzes oxidized phospholipids. Additional proatherogenic properties of elevated Lp(a) concentrations have been reported as summarized in a recent editorial. In addition, recent evidence suggests that genetic variation in the LPA locus mediated by Lp(a) concentration may also predict aortic valve stenosis.

An emerging clinical challenge to define the role of Lp(a) in CVD lies in the possibility of lowering the concentration of Lp(a) by therapies other than nicotinic acid, which may be effective, as with antisense oligonucleotides, as an inhibitor of proprotein convertase subtilisin/kexin type 9 and cholesterol ester transfer protein inhibition.

Limitations of this study include lengthy storage, which has been shown to reduce Lp(a) values modestly but would have reduced rather than increased the calculated risk. Our assay did not define the isoform pattern which bears on cardiovascular outcomes. One limitation of this current study is, therefore, the absence of Lp(a) isoform data, which may have improved the significance of an association with CHD outcomes. Most studies, with the notable exception of the Framingham Offspring Study, indicate a significantly greater association with smaller than larger isoforms.

The coefficient of variation resembled that in other studies but we cannot exclude that greater precision may have led to different degrees of significance, although the large cohort and the high levels of statistical significance support the validity of our conclusions.

In conclusion, our current study confirms a significant association between Lp(a) concentration and future cardiovascular events in patients with stable ischemic heart disease. Those associations were highly significant in a model that analyzed events among patients with substantially elevated Lp(a) values at baseline, especially those in the top decile of the distribution. A further finding was that among patients whose Lp(a) concentration increased 1 year after randomization into the study, total CHD events and total CVD events increased significantly during the following 5 years.

That period spanned the randomized part of the study and included both pravastatin- and placebo-treated groups. The prognostic value of Lp(a) at baseline and that related to change at 1 year was attributable to the concentrations in the upper decile and quartile, respectively. The recent reassessment of Lp(a) as an important CVD risk factor is supported by this study.

Acknowledgments

All authors have been members of the LIPID Management Group and have contributed to the initial trial and subsequent follow-up, including planning and interpreting the biomarker associations with future outcomes. Statistical analyses were performed at the NHMRC Clinical Trials Centre, University of Sydney. All authors have approved the manuscript.

Sources of Funding

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Disclosures

None.

References


Significance

This study of 7863 patients with stable coronary heart disease enrolled in a trial of pravastatin versus placebo (Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] study) has confirmed the status of lipoprotein(a) (Lp(a)) concentration as an independent risk factor for future cardiovascular disease events over ≥6 years. The cardiovascular risk of Lp(a) had been mostly observed previously in subjects without overt disease. The risk was especially high at Lp(a) concentrations in the top decile (>73 mg/dL) and was associated with both the baseline Lp(a) concentration and among patients whose Lp(a) concentration rose most during the first year. Baseline Lp(a) concentration was associated with total coronary heart disease events and total cardiovascular disease events (P<0.001 and P=0.002, respectively). Change in Lp(a) concentration at year 1 showed additional prognostic value for both total coronary heart disease and total cardiovascular disease events (P=0.002 for each), reinforcing the conclusion that measuring Lp(a) concentration improves risk prediction in patients with stable coronary heart disease.
Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease
Paul J. Nestel, Elizabeth H. Barnes, Andrew M. Tonkin, John Simes, Marion Fournier, Harvey D. White, David M. Colquhoun, Stefan Blankenberg and David R. Sullivan

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Methods

Study population

The design of the LIPID study has been described in detail elsewhere.¹ A total of 9014 patients from 87 centres in Australia and New Zealand were randomized to pravastatin 40 mg daily or placebo. Patients aged 31–75 years who had suffered a myocardial infarction or been hospitalized for unstable angina 3 to 36 months previously and had plasma cholesterol levels 4.0–7.0 mmol/L and triglycerides <5 mmol/L were eligible. Prespecified primary and secondary outcomes were determined, the criteria of which are shown below. Endpoints were adjudicated by a blinded outcome assessment committee, as described in the original report.¹ Baseline measurements of Lp(a) were available for 7863 patients (6530 men and 1333 women) and for most of those patients also at 1 year after randomization.

Laboratory methods

Blood was drawn after a 12-hour fast. Separated plasmas were stored at −70°C. The Lp(a) concentration was measured by Latex particle immunoassay, which was isoform independent (Abbott Diagnostics, Architect c8000). The intrarun coefficient of variation (CV) was 2.3–3.9% and interrun CV was 4.1–4.6%. The possibility that long-term storage might reduce Lp(a) levels modestly over time² might mean that the relationships described below have been weakened.

Statistical methods

The follow-up period for these analyses was a 6-year median from baseline, chosen because it represented the randomized period that included both the pravastatin- and placebo-treated cohorts.

The prespecified primary endpoints for substudies were a composite of coronary heart disease (CHD) death and nonfatal myocardial infarction during follow-up. Secondary endpoints included 1. composite of total cardiovascular (CVD) endpoints (total CVD mortality, nonfatal myocardial infarction, stroke, hospitalization for unstable angina pectoris, coronary revascularization); 2. composite of total CHD events (CHD death, nonfatal myocardial infarction, hospitalization for unstable angina, coronary revascularization).

Categorization of baseline Lp(a) took into account the robust association between extreme Lp(a) levels and cardiovascular risk reported elsewhere.³,⁴ Therefore, the categories used were: the two lowest quartiles together, the third quartile, the 75th to 90th percentile and the upper decile.

<table>
<thead>
<tr>
<th>Box 1: Covariates for adjustment in the baseline model</th>
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</thead>
<tbody>
<tr>
<td>• sex</td>
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<tr>
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<tr>
<td>• diabetes</td>
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<td>• smoking</td>
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<td>• atrial fibrillation</td>
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<tr>
<td>• estimated glomerular filtration rate</td>
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<td>• nature of prior acute coronary syndrome</td>
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<tr>
<td>• white blood cell count</td>
</tr>
<tr>
<td>• fasting glucose</td>
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<tr>
<td>• triglycerides</td>
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<tr>
<td>• peripheral vascular disease</td>
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</tbody>
</table>
Wilcoxon tests were used to compare Lp(a) levels between treatment groups. The prognostic value of Lp(a) concentration on each outcome was assessed by fitting Cox proportional-hazards time-to-event models after adjustment for the covariates shown in Box 1. These were chosen on the basis of a previous analysis of LIPID study data.5

A landmark model was fitted using only those subjects who remained event-free 1 year after randomization, when the Lp(a) measurement was repeated. The prognostic value of the change in Lp(a) between baseline and year 1 on events after year 1 was assessed on a quartile distribution of change in Lp(a) using Cox regression in a model that incorporated the covariates in Box 1 and also baseline Lp(a) levels.

With respect to the analysis of change in Lp(a) levels that required two measurements, the data were reanalyzed to take into account analytical variation.6 Based on a CV of 4.6%, the relative change of approximately 13% was the critical change larger than could be explained by analytical variation. Individual subjects were categorized according to whether their year 1 Lp(a) measurement was within 13% of their baseline level. These categories were used in models from a landmark of 1 year that were adjusted, as in the other models, for baseline clinical risk factors, which included baseline total cholesterol and high-density lipoprotein cholesterol (HDL-c). In order to examine whether a change in Lp(a) remains independently associated with events when change in low-density lipoprotein cholesterol (LDL-c) is included, further 1-year landmark models using the Lp(a) change categories described above were performed and adjusted for baseline Lp(a) and the clinical risk factors, but baseline LDL-c was substituted for HDL-c and also change in LDL-c in quartiles was added.

References