Lipoprotein(a) Is an Independent Risk Factor for Cardiovascular Disease in Hemodialysis Patients

Michael D. Cressman, DO; Robert J. Heyka, MD; Emil P. Paganini, MD; June O’Neil; Christine I. Skibinski, MS; and Henry F. Hoff, PhD

**Background.** Although serum lipoprotein(a) [Lp(a)] is an independent risk factor for atherosclerosis in the general population and Lp(a) levels are increased in hemodialysis patients, an association of Lp(a) with the risk of clinical events attributed to atherosclerosis has not been established in the chronic hemodialysis patient population. We therefore determined the association between Lp(a) levels and the risk of clinical events of presumed atherosclerotic etiology in a prospective study of an outpatient hemodialysis population.

**Methods and Results.** Lp(a) was measured by radioimmunoassay in a baseline cardiovascular disease risk assessment in a consecutive series of 129 hemodialysis patients. The relation between baseline Lp(a) and clinical events of presumed atherosclerotic etiology was determined during 48 months of follow-up. Hemodialysis patients had a median Lp(a) concentration that was approximately four times as high as the median Lp(a) concentration in normal controls and twice as high as the levels in controls with angiographic evidence of coronary artery disease [median Lp(a), 38.4 versus 16.9 mg/dl; \( p < 0.001 \)]. Baseline Lp(a) levels were no different in participants with or with no history of a previous clinical event at the time of the baseline examination. However, baseline Lp(a) concentration \( (p < 0.001) \) and a history of atherosclerotic clinical events \( (p = 0.001) \) were associated with clinical events during the period of follow-up. In contrast, baseline serum total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, age, gender, race, or duration of hemodialysis were unrelated to this risk in the prospective study. Stepwise multiple logistic regression analysis demonstrated that serum Lp(a) concentration \( (p = 0.001) \) and the presence of a previous clinical event \( (p = 0.004) \) were the only independent contributors to the risk of a clinical event during the period of follow-up.

**Conclusions.** Lp(a) is an independent risk factor for clinical events attributed to atherosclerotic cardiovascular disease in patients receiving chronic hemodialysis treatment of end-stage renal disease. (Circulation 1992;86:475–482)

**KEY WORDS** • renal disease, end-stage • survival • lipoproteins • triglycerides

Patients receiving hemodialysis treatment for end-stage renal failure frequently have abnormalities in lipoprotein structure and metabolism and have a high incidence of cardiovascular disease.\(^1\,^2\,^3\) Increased levels of several atherogenic lipoproteins, including chylomicron remnants, \( \beta \)-migrating very low density lipoproteins, and structurally modified low density lipoproteins (LDL), have been demonstrated in patients with chronic renal failure. However, LDL cholesterol (LDL-C) levels are usually normal, and an association of blood lipid, lipoprotein, or apoprotein (apo) concentrations with the risk of atherosclerosis has not been established in prospective studies of hemodialysis patients.\(^1\,^4\,^5\) Lipoprotein(a) [Lp(a)] is a cholesterol-rich lipoprotein with structural similarities to LDL\(^6\) but contains apo(a), a glycoprotein with sequence homology to plasminogen.\(^6\) Lp(a) is an independent risk factor for stroke,\(^7\) myocardial infarction,\(^8\,^9\) and the obstruction of saphenous vein bypass grafts to the coronary arteries that occurs a few years after coronary artery bypass surgery.\(^10\) Lp(a) has been demonstrated in atherosclerotic lesions of saphenous vein bypass grafts and native coronary arteries in a distribution similar to LDL.\(^11\,^12\) Taken together, these findings suggest that Lp(a) plays a causal role in the development of atherosclerosis and is a potentially modifiable cardiovascular disease risk factor. Recently, increased Lp(a) levels have been reported in case-control studies of hemodialysis patients.\(^14\,^15\)

We instituted this investigation of Lp(a) as a risk factor for clinical events attributed to atherosclerosis in a prospective study of 129 hemodialysis patients. A preliminary evaluation of a subset of this hemodialysis patient population confirmed observations of increased Lp(a) levels reported in case-control studies.\(^14\,^16\) For
this reason, we elected to observe a larger series of hemodialysis patients in a prospective study to determine if serum Lp(a) concentrations were associated with the risk of sustaining clinical events later in the course of treatment. Our study population, like the population of patients currently receiving hemodialysis in the Medicare-sponsored end-stage renal disease treatment program in the United States, is older and has a high prevalence of preexisting cardiovascular disease.17 The principal objective of the present study was to determine if serum Lp(a) concentrations were related to the risk of fatal or nonfatal events later in the course of hemodialysis treatment. We were particularly interested in determining if measurement of Lp(a) levels provided information about the subsequent risk of sustaining a clinical event of presumed atherosclerotic origin in addition to the currently recommended assessment used to evaluate cardiovascular disease risk in adults with hypercholesterolemia.18

**Methods**

**Study Design and Patients**

The study was initiated with a consecutive series of 129 adults reporting for maintenance hemodialysis treatment in the outpatient dialysis centers of the Cleveland Clinic Foundation. A history, physical examination, and routine laboratory evaluation was performed at entry to determine the relation between Lp(a) and demographic features, clinical evidence of atherosclerosis, conventional cardiovascular disease risk factors, indices of renal function, or the metabolic abnormalities that occur in patients with end-stage renal disease. Baseline characteristics of the 44 black and 85 white hemodialysis patients are summarized in Table 1. Their ages ranged from 23 to 86 years (mean, 58±14 years); hemodialysis treatment was initiated 1–217 months (mean, 50±45 months; median, 33 months) before the baseline evaluation. Definitions of conventional risk factors provided in the Adult Treatment Panel of the National Cholesterol Education Program report were used for our baseline cardiovascular disease risk assessment.18 We applied stringent criteria for the classification of cardiovascular status at entry to minimize the inclusion of patients with nonatherosclerotic cardiovascular diseases (hemorrhagic stroke, hypertensive heart disease, uremic pericarditis, vascular access–related disorders) in participants with “atherosclerotic clinical events” before entry as a risk factor for subsequent clinical events in the prospective study. Patients with a documented history of nonhemorrhagic stroke, carotid endarterectomy, myocardial infarction, coronary bypass surgery, percutaneous transluminal coronary angioplasty, severe renal artery stenosis, or lower extremity or aortic revascularization were considered to have preexisting clinical events for the purpose of this study. Approximately 30% of our hemodialysis study population had a history or evidence of one or more of these events at entry into the prospective study (Table 2).

**Biochemical Methods**

Evaluation of the relation between Lp(a) levels and indices of renal function or other metabolic alterations that accompany chronic renal failure included measurement of serum blood urea nitrogen, creatinine, calcium, phosphorus, parathyroid hormone, albumin, and glucose concentrations. A complete blood count and automated serum chemistry profile are obtained during the monthly clinical and laboratory evaluation that is performed in all patients in our maintenance hemodialysis treatment program. These specimens were obtained after a 12–14-hour fast before heparinization or initiation of hemodialysis treatment. Hemodialysis was performed 3–4 hours per session, two to three times per week. Whole blood was permitted to clot at room temperature before serum was separated from formed elements by low-speed centrifugation in a refrigerated centrifuge. Blood lipid and apoprotein measurements were performed in serum samples. Total cholesterol (TC) and triglyceride (TG) levels were measured by automated enzymatic procedures described in the Lipid Research Clinics’ manual of operations.19 Total HDL-C, HDL\(_2\)-C, and HDL\(_3\)-C concentrations were determined with a differential dextran-sulfate/Mg\(^{2+}\) precipitation technique.20 LDL-C was calculated using the Friedewald formula21 if fasting triglyceride levels were less than 400 mg/dl or by ultracentrifugation if triglyceride levels exceeded 400 mg/dl. Apo B and apo A-I were measured by electroimmunoassay.22

**Table 1. Baseline Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>129</td>
</tr>
<tr>
<td>Mean</td>
<td>58±14</td>
</tr>
<tr>
<td>Range</td>
<td>23–86</td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
</tr>
<tr>
<td>Etiology of renal disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>18%</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
</tr>
<tr>
<td>Chronic pylonephritis</td>
<td>9%</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>12%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10%</td>
</tr>
<tr>
<td>Duration of hemodialysis</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>50±45 months</td>
</tr>
<tr>
<td>Range</td>
<td>1–217 months</td>
</tr>
<tr>
<td>Median</td>
<td>33 months</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>44</td>
</tr>
<tr>
<td>White</td>
<td>85</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>83%</td>
</tr>
<tr>
<td>Low high density lipoprotein cholesterol</td>
<td>53%*</td>
</tr>
<tr>
<td>Previous event</td>
<td>27%</td>
</tr>
<tr>
<td>Family history</td>
<td>18%</td>
</tr>
<tr>
<td>Smoking</td>
<td>15%</td>
</tr>
<tr>
<td>High-risk low density lipoprotein cholesterol</td>
<td>10%*</td>
</tr>
<tr>
<td>Male</td>
<td>49%</td>
</tr>
</tbody>
</table>

*High density lipoprotein cholesterol, <0.91 mmol/l or <35 mg/dl.

†Low density lipoprotein cholesterol, ≥4.14 mmol/l or ≥160 mg/dl.
TABLE 2. Classification of Cardiovascular Disease Status at Entry

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic brain infarction</td>
<td>14</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>1</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Documented in hospital</td>
<td>17</td>
</tr>
<tr>
<td>ECG evidence only</td>
<td>14</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>6</td>
</tr>
<tr>
<td>Percutaneous coronary angioplasty</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Lower-extremity revascularization</td>
<td>5</td>
</tr>
<tr>
<td>Total no. of events</td>
<td>61</td>
</tr>
<tr>
<td>No. of patients with events</td>
<td>37</td>
</tr>
</tbody>
</table>

Serum samples for Lp(a) measurements were stored at
−70°C. Lp(a) was measured by a previously described
double-antibody radioimmunoassay for apo(a) using
polyclonal antibodies obtained by immunizing goats with
purified human Lp(a) from a single donor with a high
Lp(a) concentration.10 Contaminating anti–apo B anti-
bodies were removed with an LDL-Sepharose column to
obtain purified goat anti-human apo(a) antibodies. Iodi-
nation for the Lp(a) assay was performed by the mono-
chloride method described by Bilheimer and others.23
The purified Lp(a) used in the Lp(a) assay were also
obtained from a single donor with high Lp(a) level.
Intra-assay and interassay coefficients of variation were
less than 5% and 10–15%, respectively. Lp(a) levels are
expressed in milligrams per deciliter of lipoprotein mass.

Follow-up in Prospective Study

The requirement for patients to return to the dialysis
center two or three times per week for hemodialysis
treatment facilitated determination of clinical end
points that were used to determine the association of
baseline Lp(a) concentration with the risk of atheroscle-
rotic clinical events during the 48-month follow-up
period. The classification of cardiovascular status at
entry (Table 2) was used to classify fatal and nonfatal
clinical events into atherosclerotic and nonatheroscle-
rotic etiologies. Patients with a hospital discharge diag-
nosis of “stroke” were considered to have a clinical
event if radiographic evidence of a nonhemorrhagic
cerebral infarction was demonstrated during an in-
patient evaluation of a participant with recent onset
focal cerebrovascular disease symptoms. This distinc-
tion was made since intracerebral hemorrhage is rela-
tively common in hemodialysis patients but may be due to
poorly controlled hypertension, heparinization during
hemodialysis treatment, or other hemostatic defects
that occur in hemodialysis patients.2,5,24 The diagnosis
of myocardial infarction required the presence of a new Q
wave myocardial infarction on the 5-year ECG or
documentation of acute myocardial infarction by enzy-
matic and/or ECG criterion during a hospital admis-
sion. Coronary bypass surgery or percutaneous translu-
minal angioplasty of the coronary arteries were also
considered to be definite evidence of coronary ather-
sclerosis. Surgical treatment of carotid, aortoiliac, or
lower-extremity atherosclerosis was also classified as a
clinical event considered to be atherosclerotic in origin.

An independent panel of nephrologists who were
blinded to Lp(a) levels classified the etiology of fatal
events that occurred during the prospective study. This
hemodialysis mortality review committee is an estab-
lished component of our outpatient end-stage renal
failure treatment program. The category of uncertain
cause of death in this classification system included
unwitnessed deaths occurring outside of the hospital
setting, voluntary withdrawal of hemodialysis, deaths
attributed to noncardiovascular disorders or multiorgan
system failure, hyperkalemia, acute neurological events,
and unknown causes of death. Thus, an uncertain cause
of death was considered to be present if a clear athero-
sclerotic or noncardiovascular cause of death (e.g.,
massive gastrointestinal hemorrhage, sepsis, or meta-
static malignancy) could not be established.

Statistical Analysis

Data analysis was performed using the Statistical
Analysis System (SAS) software package (Cary, N.C.)
using Wilcoxon’s rank-sum tests or Student’s t tests for
group comparisons of continuous variables with nonnor-
mal or normal population distributions, respectively.25
Spearman correlation coefficients were determined to
evaluate the relation between Lp(a) and other continu-
ous variables. χ² tests or Fisher’s exact tests were
performed to examine the relation between baseline
risk parameters and clinical events using the categori-
cal definitions of conventional risk factors recommended in
the Adult Treatment Panel of the National Cholesterol
Education Program report.18 Age and white race were
included as potential risk factors in this analysis since
they have been associated with cardiovascular disease
risk in previous studies of hemodialysis patients.1,2,17
However, age, duration of hemodialysis treatment,
baseline TC, TG, HDL-C, LDL-C, and Lp(a) levels
were analyzed as continuous variables and compared in
patients who experienced a clinical event with the
remaining patients who did not experience a clinical
event during the period of follow-up. Baseline param-
eters with a p < 0.3 level of significance on univariate
analysis were entered into stepwise multiple logistic and
Cox regression analyses to determine their independent
association in the presence of other significant baseline
risk factors with clinical events during the period of
follow-up. Kaplan–Meier event-free survival curves
(survival with no clinical events) were analyzed sepa-
rately in participants with baseline Lp(a) levels above
and below 38.4 mg/dl [the median baseline Lp(a) level]
and compared using the log-rank test. The sensitivity,
specificity, and predictive values (negative and positive)
for the median Lp(a), LDL-C, or HDL-C concentra-
tions were also determined. Receiver operating charac-
teristic (ROC) analysis was performed to evaluate mul-
tiple cutoff points for the Lp(a) clinical event–risk
relation.26 The number and percentage of participants
with baseline Lp(a) concentrations in each quartile of
the Lp(a) population were also determined and ana-
lyzed for association of each Lp(a) quartile cutoff point
to clinical events in the prospective study. Linearity of
log odds ratios was also analyzed to determine if a
continuous relation between Lp(a) and clinical events was present in the prospective study.

Results

Baseline Findings

The population distribution of Lp(a) values in our hemodialysis patients is provided in Figure 1. The median Lp(a) concentration of 38.4 mg/dl for the hemodialysis group compares with median Lp(a) concentrations of approximately 8 mg/dl in published studies of white control populations.27,28 The distribution of Lp(a) values in our hemodialysis group was far less skewed than the Lp(a) distribution of healthy controls or our control population of coronary artery disease and normal renal function.27-28 Because a substantial number of our hemodialysis patients had clinical evidence of atherosclerosis at entry, we compared our study population with this age-matched group of controls with no history of chronic renal failure but angiographically documented coronary artery disease (Figure 1, upper panels). Hemodialysis study participants had Lp(a) levels that were twice as high as the levels in controls [median Lp(a), 38.4 versus 16.9 mg/dl, p<0.001].

Blacks have also been shown to have Lp(a) levels that are twice as high as the levels in whites.29 For this reason, we considered the possibility that inclusion of blacks (n=44) could have accounted for the apparent increase in Lp(a) values in our hemodialysis study population. As seen in Figure 1 (lower panels), the median Lp(a) concentration in black hemodialysis patients was higher than the Lp(a) concentration in white hemodialysis patients (49.1 versus 34.1 mg/dl, p=0.01). However, white hemodialysis patients had Lp(a) levels that were still twice as high as the levels in white controls with coronary artery disease (34.1 versus 16.9 mg/dl, p<0.001). In contrast to this association of Lp(a) concentration with race, Lp(a) levels were unrelated to age, gender, duration of hemodialysis treatment, percent ideal body weight (%IBW), TG, HDL-C, LDL-C, apo B, or apo A-I levels at entry (Table 3). In addition, no relation between baseline Lp(a) concentration and the presence of a preexisting clinical event was observed at entry into the prospective study. Baseline Lp(a) concentrations were unrelated to the duration of hemodialysis treatment before entry, indices of "uremic control," or any other parameters analyzed during the baseline evaluation. The lack of association between Lp(a) concentration and duration of hemodialysis treatment suggests that a progressive increase or reduction of Lp(a) concentration does not occur during prolonged hemodialysis treatment (Table 4).

Our interest in the association of baseline Lp(a) values with the risk of subsequent clinical events prompted an evaluation of the variability of Lp(a) concentrations before and after 1 year of follow-up in a subset (n=8) of our hemodialysis study participants. Baseline and 1-year Lp(a) levels were closely related (r=0.97, p<0.001) with a coefficient of variation of 16% between the baseline and repeat Lp(a) levels. This is similar to the 10-15% interassay coefficient of variation for our Lp(a) assay and indicates that biological variability of Lp(a) concentrations is minimal during maintenance hemodialysis treatment. For this reason, use of a single baseline Lp(a) measurement appeared to provide a reliable estimate of Lp(a) values on repeat testing 1 year later and a reasonable estimate of the "true" Lp(a) value during the prospective study.30

Follow-up and Clinical Events

Follow-up was complete for the 129 patients who experienced 26 clinical events attributed to atheroscle-
rosis (20 fatal and six nonfatal) during the 48-month period of observation (Tables 4–6). Twenty-four additional deaths were noncardiovascular (n=11) or of uncertain cause (n=13). Nineteen patients discontinued hemodialysis treatment after successful renal transplantation. None of these patients had a nonfatal clinical event before or after renal transplantation. Baseline TC, TG, HDL-C, LDL-C, and Lp(a) levels in the 26 participants with clinical events and the 103 individuals who did not experience one of these events are provided in Table 5. The 60 survivors who continued hemodialysis treatment at the conclusion of the study had similar TC, TG, HDL-C, LDL-C, and Lp(a) levels compared with the remaining hemodialysis patients who underwent renal transplantation or experienced a fatal event not attributed to atherosclerosis. Lp(a) levels were higher in the 26 patients with a clinical event than in the entire population of 103 study participants who did not experience a clinical event during the period of follow-up (p<0.001). As seen in Table 5, a significant overall difference in Lp(a) levels was present between participants who experienced a clinical event, uncertain cause of death, individuals who received a renal transplant, or the 60 survivors who continued hemodialysis at the conclusion of the study (p=0.002). Significant pairwise differences were present between the patients with clinical events and the renal transplant patients, patients with noncardiovascular deaths, and the clinical event-free survivors.

A stepwise increase in the risk of a clinical event was observed (Table 4) in participants with quartiles 1–4 baseline Lp(a) levels (p<0.001). In contrast, duration of hemodialysis before entry or total duration of hemodialysis (before and after entry) were unrelated to the

### Table 4. Duration of Hemodialysis Treatment, Serum Lp(a) Concentration, and the Risk of Clinical Events Attributed to Atherosclerotic Cardiovascular Disease

<table>
<thead>
<tr>
<th>Previous duration of HD (before entry) quartile (months)</th>
<th>Median Lp(a) (mg/dl)</th>
<th>No. of events</th>
<th>% of events</th>
<th>Median total duration of HD (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–18</td>
<td>39.4</td>
<td>8</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>19–32</td>
<td>45.2</td>
<td>5</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>33–68</td>
<td>35.6</td>
<td>8</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>69–217</td>
<td>46.6</td>
<td>5</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Total duration of HD (before and after entry) quartile (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–45</td>
<td>38.9</td>
<td>8</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>46–68</td>
<td>42.8</td>
<td>9</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>69–104</td>
<td>36.1</td>
<td>5</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>105–254</td>
<td>43.6</td>
<td>4</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>Baseline Lp(a) (mg/dl) quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>1</td>
<td>3.8*</td>
<td>78.5</td>
<td></td>
</tr>
<tr>
<td>15–38.3</td>
<td>5</td>
<td>19.2*</td>
<td>67.0*</td>
<td></td>
</tr>
<tr>
<td>38.4–73.1</td>
<td>6</td>
<td>23.1*</td>
<td>73.5</td>
<td></td>
</tr>
<tr>
<td>&gt;73.1</td>
<td>14</td>
<td>53.8*</td>
<td>68.0</td>
<td></td>
</tr>
</tbody>
</table>

* Lp(a), lipoprotein(a); HD, hemodialysis. *p<0.001, χ² test for trend.

### Table 5. Lipid and Lp(a) Levels in Patients With Atherosclerotic Events or With No Atherosclerotic Events

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>TC (mmol/l±SD)</th>
<th>TG (mmol/l±SD)</th>
<th>HDL-C (mmol/l±SD)</th>
<th>LDL-C (mmol/l±SD)</th>
<th>Median Lp(a) (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with clinical events</td>
<td>26</td>
<td>4.83±1.36</td>
<td>2.25±1.82</td>
<td>0.99±0.46</td>
<td>2.86±1.14</td>
</tr>
<tr>
<td></td>
<td>(186 mg/dl)</td>
<td>(199 mg/dl)</td>
<td>(33 mg/dl)</td>
<td>(110 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Patients with no clinical events</td>
<td>103</td>
<td>4.52±1.25</td>
<td>2.08±1.38</td>
<td>0.93±0.38</td>
<td>2.66±0.98</td>
</tr>
<tr>
<td></td>
<td>(175 mg/dl)</td>
<td>(184 mg/dl)</td>
<td>(36 mg/dl)</td>
<td>(103 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>19</td>
<td>3.96±0.95</td>
<td>1.40±0.89</td>
<td>1.04±0.50</td>
<td>2.28±0.68</td>
</tr>
<tr>
<td></td>
<td>(153 mg/dl)</td>
<td>(124 mg/dl)</td>
<td>(40 mg/dl)</td>
<td>(88 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular deaths</td>
<td>11</td>
<td>4.32±1.20</td>
<td>1.76±1.16</td>
<td>1.06±0.31</td>
<td>2.81±1.07</td>
</tr>
<tr>
<td></td>
<td>(168 mg/dl)</td>
<td>(167 mg/dl)</td>
<td>(41 mg/dl)</td>
<td>(108 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Uncertain deaths</td>
<td>13</td>
<td>4.50±1.22</td>
<td>2.21±1.59</td>
<td>0.86±0.31</td>
<td>2.64±0.92</td>
</tr>
<tr>
<td></td>
<td>(174 mg/dl)</td>
<td>(196 mg/dl)</td>
<td>(33 mg/dl)</td>
<td>(93 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Survivors with no events</td>
<td>60</td>
<td>4.74±1.32</td>
<td>2.33±1.44</td>
<td>0.89±0.36</td>
<td>2.75±1.04</td>
</tr>
<tr>
<td></td>
<td>(183 mg/dl)</td>
<td>(206 mg/dl)</td>
<td>(34 mg/dl)</td>
<td>(106 mg/dl)</td>
<td></td>
</tr>
</tbody>
</table>

*Pairwise comparison vs. clinical events, p<0.003.
'Clinical vs. no clinical events, p<0.001.
Overall comparison of patients with clinical events and four subsets of the 103 participants with no clinical events, p=0.002.
TABLE 6. Stepwise Multiple Logistic Regression Analysis of Risk Factors for Clinical Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$</th>
<th>SEM</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.1545</td>
<td>0.5352</td>
<td>1.02</td>
<td>(1.01, 1.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>0.0230</td>
<td>0.0068</td>
<td>1.02</td>
<td>(0.48, 3.36)</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous event</td>
<td>1.4231</td>
<td>0.5014</td>
<td>4.15</td>
<td>(1.55, 11.09)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Addition*

- Male gender
- Hypertension
- Diabetes mellitus
- History of smoking
- Family history
- Obesity
- White race
- Age at baseline
- Age at event
- HDL-C
- Total cholesterol
- LDL-C
- Total time on HD

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HD, hemodialysis.

*Addition of baseline risk parameters to the model.

Risk of sustaining a clinical event. There was no evidence of a “threshold” effect of Lp(a) as a risk factor for clinical events based on linearity of log odds ratios or with ROC analysis of multiple Lp(a) cutoff points. TC, TG, HDL-C, LDL-C, Lp(a), age, and duration of hemodialysis treatment were analyzed as continuous variables in a stepwise logistic and Cox regression analysis. The logistic and Cox regression models produced similar results when total duration of hemodialysis (before and during the prospective study) was used in the logistic model and duration of hemodialysis before entry was used in the Cox model. Baseline Lp(a) concentration and the presence or absence of preexisting evidence of an atherosclerotic clinical event were the only independent contributors to risk in these regression models. Male gender, hypertension, diabetes mellitus, smoking history, family history of premature coronary heart disease, obesity, and white race were entered into the stepwise logistic models as categorical variables to determine their contribution to risk. As seen in Table 6, this stepwise analysis demonstrated that a 1-mg/dl or 10-mg/dl increment in Lp(a) concentration was associated with a 1.02 or 1.26 increase, respectively, in the relative risk of sustaining an event ($p=0.001$). The presence of a previous clinical event was also the only parameter that contributed to the stepwise multiple logistic regression model ($p=0.004$) after adjustment for the influence of baseline Lp(a) concentration. The expected trend toward an association between age and the risk of a clinical event was observed ($p=0.10$ for age at baseline; $p=0.19$ for age at the time of an event or conclusion of the 48-month study), but duration of hemodialysis ($p=0.28$) or race ($p=0.28$) did not improve the risk assessment provided by Lp(a) and presence of a previous clinical event in this stepwise model.

Median Lp(a) concentration had greater sensitivity, specificity, and predictive values as a marker for clinical events than did median LDL-C or HDL-C levels (Table 7). Using the median Lp(a) concentration of 38.4 mg/dl as an arbitrary cutoff point to define “increased Lp(a)” concentration, separation of survival curves was noted after approximately 18 months of observation in the prospective study (Figure 2). Overall, the Kaplan-Meier survival curves were significantly different ($p=0.021$) by the log-rank test in these groups.

**Discussion**

The potential role of Lp(a) as a risk factor for atherosclerosis in hemodialysis patients was first suggested by Parra et al in 1987. The median Lp(a) concentration in Parra et al’s hemodialysis patients was similar to the levels noted in our white hemodialysis

TABLE 7. Sensitivity, Specificity, and Predictive Values of Lp(a), LDL-C, and HDL-C for Atherosclerotic Events

<table>
<thead>
<tr>
<th>ROC*</th>
<th>Median</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value (positive test)</th>
<th>Predictive value (negative test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>34.8 mg/dl</td>
<td>73.1</td>
<td>56.3</td>
<td>29.7</td>
<td>89.2</td>
</tr>
<tr>
<td>LDL-C</td>
<td>2.51 mmol/l (97 mg/dl)</td>
<td>53.8</td>
<td>49.5</td>
<td>21.2</td>
<td>81.0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.85 mmol/l (33 mg/dl)</td>
<td>50</td>
<td>48.5</td>
<td>19.7</td>
<td>79.4</td>
</tr>
</tbody>
</table>

Lp(a), lipoprotein(a); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

*Receiver operating characteristics (ROC).

$p<0.001$ for area under the curve of Lp(a) compared with LDL-C or HDL-C ROC curve.
study participants and in the case–control study of hemodialysis patients reported by Parsy et al.\textsuperscript{15} Our white controls with angiographic documentation of coronary artery disease had Lp(a) levels that were twice as high as the levels in Parra et al’s and Parsy et al’s controls or in the healthy white controls reported by other investigators.\textsuperscript{14,15,27–29} For this reason, the increased Lp(a) levels observed in hemodialysis patients cannot be entirely explained by the increased Lp(a) concentrations present in a population of patients with coronary artery disease.\textsuperscript{7–10,28,29} We did not observe an association between Lp(a) concentration and the presence of preexisting clinical events in our baseline analysis, which is also consistent with the observation of Parsy and coworkers, who used clinical evidence of lower-extremity atherosclerosis as their “clinical atherosclerotic events.” Thus, the finding of an independent relation between baseline Lp(a) concentration and the risk of developing a clinical event in our prospective study contrasts with observations made in Parsy et al’s study as well as in the baseline evaluation of our hemodialysis patients.

One limitation of data obtained in a cross-sectional analysis of hemodialysis patients relates to the inability to document that Lp(a) elevations preceded development of the clinical events considered to be end points of atherosclerosis. We cannot be certain if our hemodialysis patients with elevated Lp(a) levels at entry had increased levels before hemodialysis was instituted because predialysis Lp(a) measurements were not obtained. If the elevated Lp(a) values in our hemodialysis study participants represent a metabolic complication of renal failure, any clinical event that occurred before renal failure was established would not be related to the baseline Lp(a) concentrations obtained in the present study. Thus, the discrepancy between our baseline and prospective analyses of the relation between Lp(a) and clinical events could be viewed as evidence consistent with a metabolic complication of renal failure or hemodialysis treatment as the explanation for elevated Lp(a) values. In contrast to the uncertainty regarding the temporal relation between Lp(a) levels and clinical events in the baseline evaluation, we established that the baseline Lp(a) measurements obtained in our study did not change over a 1-year period of observation in the subset of patients who had repeat Lp(a) measurements. Our baseline findings also suggest that no major increase or reduction of Lp(a) levels occurs during prolonged hemodialysis treatment. The variability of the baseline and 1-year Lp(a) measurements was similar to the interassay coefficient of variation for the Lp(a) assay in our laboratory.\textsuperscript{10} Thus, stability of Lp(a) levels during prolonged periods of observation appears to be a characteristic during hemodialysis treatment that has also been observed in normal individuals.\textsuperscript{17}

Although the marked elevation of Lp(a) levels in our white hemodialysis patients compared with our white coronary artery disease controls is indirect evidence that genetic factors do not completely explain the elevated Lp(a) levels observed in our hemodialysis patient population, the possibility that renal failure or hemodialysis treatment had no effect on Lp(a) levels in our study participants cannot be excluded with certainty. Thus, our findings do not eliminate a genetic cause of Lp(a) levels in the hemodialysis population. Lp(a) levels are primarily under control in the general population and inversely related to the size of apo(a) isoforms based on the apo(a) isoform phenotype determinations reported by Utermann and coworkers.\textsuperscript{27} For this reason, a marked shift in the distribution of apo(a) isoform size estimates from the predominance of larger apo(a) isoforms in healthy individuals toward smaller apo(a) isoforms in the hemodialysis population would be expected if the metabolic abnormality responsible for elevated Lp(a) was primarily genetic in origin. However, we did not determine apo(a) isoform phenotypes in our study, and no information about this relation is available in the literature. Preliminary studies were initiated at the conclusion of this 48-month prospective study to assess the potential contribution of renal failure or factors specifically related to hemodialysis treatment in an evaluation of peritoneal dialysis patients and renal transplant recipients.

Intermittent heparinization, exposure of blood to a hemodialysis membrane, or use of a specific type of solution in dialysis are examples of aspects of hemodialysis treatment that are not present in chronic ambulatory peritoneal dialysis patients or in renal transplant recipients. We did not demonstrate a relation between average weekly heparin dose and baseline Lp(a) concentrations or an association of Lp(a) level with composition of different membrane dialyzers. We recently reported that the median Lp(a) concentration was approximately 38 mg/dl in patients receiving chronic ambulatory peritoneal dialysis and 10 mg/dl in renal transplant recipients with functioning renal allografts.\textsuperscript{31} Taken together, these observations suggest that the increased Lp(a) levels observed in our hemodialysis patients represent a complication of the renal failure state rather than a specific effect of hemodialysis treatment or a primary genetic abnormality.

Although we do not consider the results of our study to represent proof that Lp(a) plays a causative role in the development or progression of atherosclerosis during hemodialysis treatment, our findings are the clearest demonstration of a lipoprotein–cardiovascular risk association reported to date. The high incidence of clini-
cal events during 48 months of hemodialysis treatment in hemodialysis patients with the highest Lp(a) values [clinical events in 54% of Lp(a) quartile 4 participants] suggests that Lp(a) measurements could be useful for identification of a subset of high-risk hemodialysis patients. This finding could also be viewed as an indication to aggressively manage other risk factors for atherosclerosis or consider early renal transplantation if marked reduction of Lp(a) levels is confirmed after renal transplantation. The availability of effective pharmacological agents or other methods to reduce Lp(a) levels in hemodialysis patients will provide the opportunity to formally test the hypothesis that Lp(a) is a modifiable risk factor for cardiovascular disease in the end-stage renal failure patient population.

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