Serum Lipoprotein(a) in Patients Heterozygous for Familial Hypercholesterolemia, Their Relatives, and Unrelated Control Populations

A.D. Mbewu, D. Bhatnagar, P.N. Durrington, L. Hunt, M. Ishola, S. Arrol, M. Mackness, P. Lockley, and J.P. Miller

Serum lipoprotein(a) (Lp[a]) levels were significantly higher in 89 patients with heterozygous familial hypercholesterolemia (FH) (geometric mean, 22.7 mg/dl) than in 109 normocholesterolemic controls (10.0 mg/dl, p<0.05) and 40 controls (9.1 mg/dl, p<0.05) with similarly elevated low density lipoprotein cholesterol levels due to other primary hypercholesterolemiases. To provide further evidence that the increased serum Lp(a) concentration was due to inheritance of the FH gene, 24 unaffected first-degree relatives were compared with their FH probands. Serum Lp(a) in affected individuals was significantly greater than in unaffected relatives (geometric means, 26.5 versus 13.7 mg/dl, respectively; p<0.05). Family membership exerted an effect on serum Lp(a) concentrations, indicating that other genetic influences were also operating, as is known to be the case in general populations. Serum Lp(a) in 30 of the FH patients, who had coronary heart disease, was not significantly different from 30 age- and sex-matched controls with FH but without coronary heart disease (geometric means, 23.6 versus 24.7 mg/dl, respectively). FH is associated with an increase in serum Lp(a). Elevated serum Lp(a) concentrations should probably now be regarded as a component of the clinical syndrome of FH. However, within our FH population Lp(a) did not distinguish those with clinically overt coronary heart disease from those without the disease. (Arteriosclerosis and Thrombosis 1991;11:940-946)

In 1963 lipoprotein(a) (Lp[a]) was discovered in human plasma by Berg.1 It is now known to be universally present, but its concentration varies widely among individuals.2,3 Interest has grown since the discovery that individuals with high Lp(a) levels develop early-onset ischemic heart disease4-6 (IHD) and cerebrovascular disease,7 although this may only be true if low density lipoprotein (LDL) levels are also high.8 Serum Lp(a) levels are largely genetically determined,9 and they explain a substantial element of family history as a risk factor for coronary artery disease.10 Lp(a) is a subfraction of LDL. The protein moiety of Lp(a) comprises a specific apolipoprotein, apolipoprotein(a) (apo[a]), which is covalently linked to apo B-100.11 Generally, the bulk of the circulating LDLs have apo B but do not have apo(a). Great interest in Lp(a) has been generated by the finding of close structural homology between apo(a) and plasminogen, the gene for which is located close to that of apo(a) on chromosome 6.12 Because of its structural similarity with plasminogen, it has been suggested that apo(a) may confer on Lp(a) a role in both thrombosis and atherogenesis.12,13 Familial hypercholesterolemia (FH) is a dominantly inherited disorder of the LDL receptor, resulting in decreased LDL catabolism, hypercholesterolemia, coronary heart disease (CHD), and tendon xanthomata. There is a considerably increased risk of CHD, which is present in 51% of men and 12% of women below the age of 50 who are heterozygotes for the condition.14 There have been two reports that Lp(a) levels are raised in patients with heterozygous FH.15,16 One study compared FH heterozygotes living in London with normolipidemic Tyrolean adults,15 and the other contrasted Swedish FH heterozygotes with normolipidemic people living in the same region.16 An increase in Lp(a) in FH patients may contribute to their high risk of CHD, and higher levels of
Lp(a) have been reported in FH patients with CHD than in those who have not developed that complication. However, two essential questions require further elucidation. First, does the increase in Lp(a) in FH occur as a result of the inheritance of the gene for FH, or is it the case that patients with FH syndrome come from families with higher than average Lp(a) levels? Second, does the high serum Lp(a) concentration result from the inheritance of the defective LDL receptor gene, or is it secondary to the increase in circulating LDL levels regardless of cause? The present study was designed to answer these questions by comparing probands with FH with both their affected and unaffected relatives and also by recruiting a control group matched for serum LDL cholesterol levels. In addition, our study design allowed us to closely match patients with and without CHD for age and sex.

Methods

Patients and Controls

Ethical consent for the study was obtained from the Medical Ethical Committee of the Manchester Royal Infirmary and the University Hospital of South Manchester. Commencing in 1988, 134 heterozygotes for FH were enrolled serially from a total of 250 patients attending two lipid clinics in Manchester. All 134 FH patients except one 12-year-old were older than 18 years of age. Of the 134 FH patients, 89 were probands and 45 were their first-degree relatives diagnosed with FH at family screening (21 were sons or daughters, 20 were siblings, and four were parents of the probands). Also in the course of family screening, 24 first-degree relatives were discovered who did not have hypercholesterolemia or features of FH (11 siblings, 12 sons or daughters, and one parent).

A questionnaire was administered by a research nurse to each proband and first-degree relative. This included details of lipid disorders, medication, chest pain, cardiovascular investigations, and a full family history. Examination included height, weight, blood pressure, and a search for tendon xanthomata. Venous blood was taken between 9 and 11 AM after fasting from 10 PM the previous day. FH was diagnosed by hypercholesterolemia, that is, serum cholesterol greater than 8 mmol/l (before the introduction of lipid-lowering drug therapy) plus tendon xanthomata in probands, and by the same criteria or by marked hypercholesterolemia alone (total serum cholesterol >8 mmol/l) in first-degree relatives. CHD was considered to be present when there was a positive exercise electrocardiogram test and/or coronary artery stenosis at angiography of more than 70% in at least one coronary artery in patients with a history of angina of effort or a history of myocardial infarction with definite electrocardiographic changes and cardiac enzyme changes. The mean age of onset of CHD in the probands was 39 years. In every case the patient was examined by a doctor who had also checked their responses to the questionnaire and reviewed their hospital notes and medical records from other hospitals. Thirty of the FH patients with CHD were matched for age (within 2 years) and gender with 30 unrelated FH patients without CHD. Normocholesterolemic controls (total serum cholesterol <6.0 mmol/l) were recruited from a healthy population attending a family practice in South Manchester and from men working in local industry. Hypercholesterolemic controls (total serum cholesterol >6.0 mmol/l) were recruited from patients already attending our lipid clinics who did not fulfill our criteria for the diagnosis of FH. The lipoprotein phenotype of all hypercholesterolemic patients studied was either IIA or IIB. More than 90% of FH patients had the IIA phenotype, whereas the hypercholesterolemic controls were about equally divided between IIA and IIB. Probands with FH and hypercholesterolemic controls were not receiving therapy with nicotinic acid or its derivatives, neomycin, or any other drug known to affect the serum Lp(a) concentration. A similar proportion of the probands and hypercholesterolemic controls (89% and 78%, respectively) were receiving either one or two lipid-lowering drugs (cholesteramyline, bezafibrate, gemfibrozil, or simvasatin). We have not found that any of these drugs has a major quantitative effect on serum Lp(a) levels (J.P. Miller et al, unpublished data).

Laboratory Methods

Very low density lipoprotein (VLDL) was isolated as the supernatant by tube slicing (Spinco tube slicer, Beckman Instruments, Palo Alto, Calif.) after ultracentrifugation of 5 ml serum overlayed with 1 ml 0.15 mol/l saline for 24 hours at 100,000 g (Beckman L8M55 ultracentrifuge with 50.3 Ti rotor). High density lipoprotein (HDL) and HDL$_{3}$ were also isolated as the infranatants in two separate tubes in which the density of serum had been adjusted to 1.063 and 1.21 g/ml, respectively, and which were ultracentrifuged at 100,000 g for 48 hours. Our laboratory participates in the UK national quality control scheme for cholesterol estimation. Cholesterol in serum and lipoproteins was determined enzymatically (reagent supplied by Diamed, Murten, Switzerland), and triglycerides were determined by the glycercyl phosphate oxidase-peroxidase-antiperoxidase method (Boehringer Mannheim, Mannheim, FRG). Within-batch coefficients of variation for cholesterol and triglyceride assays were 1.5% and 2.1%, respectively. The concentrations of cholesterol in LDL and HDL$_{3}$ were obtained by subtraction.

Apo B was determined by immunoelectrophoresis, and Lp(a) was determined by a two-site immunoradiometric assay (Pharmacia, Uppsala, Sweden) previously evaluated in this laboratory. This method shows no cross immunoreactivity with plasminogen or with LDL and has a detection limit of 0.06 mg/dl. The method was standardized against the standard provided by Pharmacia, and the results were expressed as milligrams of total protein in Lp(a) (i.e., apo[a] and apo B per deciliter of serum), which
we have confirmed (results not shown) is equivalent to Pharmacia units/l x 10\(^{-1}\). The within-batch coefficients of variation for the apo B and Lp(a) assays were 5.4% and 6.0%, respectively. In all lipid and apolipoprotein assays quality-control sera were included to ensure that between-batch variation was within acceptable limits.

**Statistics**

For two groups, the two-sample Student’s \(t\) test (two tailed) was used to compare the means of variables that were normally distributed. A logarithmic transformation was used for some variables (triglyceride, Lp[a], and VLDL concentrations) to render the data normal. Alcohol consumption was compared by use of the nonparametric Mann-Whitney \(U\) test. Qualitative variables with two categories (sex, number with IHD, smokers) were compared by use of \(2 \times 2 \chi^2\) tests.

Groups that were matched pairwise were compared by the paired Student’s \(t\) test (after logarithmic transformation in the case of Lp[a] and triglycerides). One-way analyses of variance were used to compare the means of three groups and were followed by Scheffé’s multiple-comparison procedures\(^{20}\) with a 5% level of significance. The nonparametric Kruskal-Wallis one-way analysis of variance was used for alcohol consumption, and \(3 \times 2 \chi^2\) tests were used for other variables as appropriate.

**Results**

The total population of 134 FH heterozygotes in the study were similar to their 89 probands (Table 1). Because of the family relationships within the entire study population and therefore a possible statistical dependence, we compared only the probands with the normocholesterolemic and hypercholesterolemic controls. It was clear that the probands had elevated LDL cholesterol levels compared with those of controls and that their VLDL cholesterol was also increased and the HDL cholesterol was decreased. The most striking difference between the FH population and both the normal and hypercholesterolemic controls was a greater than twofold increase in their mean serum Lp(a) concentration (Table 1).

There was no significant difference between the sexes in serum Lp(a) concentrations in FH and no correlation between serum Lp(a) and advancing age (Kendall’s \(\tau = -0.02, p=NS\)).

Some similarity was observed among Lp(a) levels of FH patients within the same families. We therefore analyzed the Lp(a) levels statistically with a one-way analysis of variance while regarding family as a random effect. The ratio of the between-family to the within-family mean squares was statistically significant \((p<0.001)\), indicating a significant family effect. It was estimated that between-family variation accounted for 46% of the total variation. Family membership was thus an important influence on individual Lp(a) values.

To investigate whether the high serum Lp(a) concentration in FH segregated with the FH gene or whether FH was prevalent in families with high Lp(a) values, 24 unaffected first-degree relatives of FH patients were compared with their probands (Table 2). The statistical analyses shown were for paired results; unpaired analyses gave similar results. The expected differences in serum cholesterol, LDL cholesterol, and apo B were evident as was a slight increase in triglycerides and a decrease in HDL cholesterol in the probands. These latter two observations may relate to the much higher rate of CHD in the probands and thus to the well-known effect of treatment with \(\beta\)-adrenoceptor-blocking drugs on triglycerides and HDL.\(^{21}\) However, independent effects of FH on both HDL and triglycerides have been

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**Table 1. Serum Lipid, Lipoprotein, and Lipoprotein(a) Concentrations in Men and Women With Familial Hypercholesterolemia, Related and Unrelated, in Unrelated Familial Hypercholesterolemia Probands, in Controls With Normal Serum Lipid Levels, and in Controls With Hypercholesterolemia Not Due to Familial Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All FH heterozygotes</th>
<th>FH probands</th>
<th>Normocholesterolemic controls</th>
<th>Hypercholesterolemic controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N or n) (M:F)</td>
<td>134 (65:69)</td>
<td>89 (51:38)</td>
<td>103 (77:26)</td>
<td>40 (31:9)</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>42 (12–68)</td>
<td>45 (18–67)</td>
<td>49 (20–74)†</td>
<td>53 (26–69)‡</td>
</tr>
<tr>
<td>Quetelet’s index (kg/m(^2))</td>
<td>24.2±3.4</td>
<td>24.7±3.4</td>
<td>24.6±3.0</td>
<td>26.2±3.4</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>8.74±2.6</td>
<td>8.95±2.88</td>
<td>5.85±0.89‡</td>
<td>8.53±1.76</td>
</tr>
<tr>
<td>Serum triglyceride (mmol/l)†</td>
<td>1.22 (0.10–6.67)</td>
<td>1.29 (0.10–6.67)</td>
<td>1.13 (0.25–3.79)§</td>
<td>2.27 (0.43–9.30)‡</td>
</tr>
<tr>
<td>VLDL cholesterol (mmol/l)†</td>
<td>0.35 (0.02–2.55)</td>
<td>0.35 (0.02–2.55)</td>
<td>0.17 (0.04–0.65)§</td>
<td>0.56 (0.07–2.45)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>6.97±2.57</td>
<td>7.27±2.88</td>
<td>4.41±1.02‡</td>
<td>6.34±2.20</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.27±0.36</td>
<td>1.24±0.38</td>
<td>1.39±0.32‡</td>
<td>1.26±0.35</td>
</tr>
<tr>
<td>HDL(_L) cholesterol (mmol/l)</td>
<td>0.58±0.30</td>
<td>0.56±0.29</td>
<td>0.67±0.31</td>
<td>0.67±0.34</td>
</tr>
<tr>
<td>HDL(_H) cholesterol (mmol/l)</td>
<td>0.73±0.24</td>
<td>0.71±0.25</td>
<td>0.73±0.23</td>
<td>0.59±0.16</td>
</tr>
<tr>
<td>Serum Lp(a) (mg/dl)†</td>
<td>20.5 (0.9–199.8)</td>
<td>22.7 (1.0–199.8)</td>
<td>10.0 (0.8–87.4)‡</td>
<td>9.1 (0.6–75.6)‡</td>
</tr>
</tbody>
</table>

All values are mean±SD except those for age (mean and [range]) and \(\dagger\) serum triglyceride, VLDL cholesterol, and serum Lp(a) (geometric mean and [range]).

FH, familial hypercholesterolemia; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Lp(a), lipoprotein(a).

*Significantly different from FH probands by Scheffé’s method \((p<0.05)\).
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Table 2. Some Clinical Features and Serum Lipid, Lipoprotein, and Apolipoprotein Concentrations in Familial Hypercholesterolemia Heterozygotes With Unaffected First-Degree Relatives and in Unaffected Relatives

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH probands</th>
<th>Unaffected relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M:F)</td>
<td>24 (16:18)</td>
<td>24 (9:15)</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>48 (27–67)</td>
<td>36 (18–68)</td>
</tr>
<tr>
<td>CHD (%)</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>Cigarette smokers (%)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Alcohol consumption (units/week)*</td>
<td>10 (0–40)</td>
<td>4 (0–80)</td>
</tr>
<tr>
<td>Quetelet’s index (kg/m²)</td>
<td>23.9±4.1</td>
<td>23.4±3.9</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>137±20</td>
<td>124±21†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79±8</td>
<td>77±12</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)†</td>
<td>8.66±2.07</td>
<td>5.56±1.01§</td>
</tr>
<tr>
<td>Serum triglyceride (mmol/l)</td>
<td>1.27 (0.51–3.11)</td>
<td>0.99 (0.61–2.30)‡</td>
</tr>
<tr>
<td>VLDL cholesterol (mmol/l)†</td>
<td>0.36 (0.10–1.90)</td>
<td>0.33 (0.13–1.20)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>7.09±2.35</td>
<td>3.72±0.94</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.16±0.36</td>
<td>1.43±0.33§</td>
</tr>
<tr>
<td>HDL₃ cholesterol (mmol/l)</td>
<td>0.49±0.30</td>
<td>0.69±0.34</td>
</tr>
<tr>
<td>HDL₄ cholesterol (mmol/l)</td>
<td>0.68±0.25</td>
<td>0.75±0.25</td>
</tr>
<tr>
<td>Serum Lp(a) (mg/dl)†</td>
<td>26.5 (1.5–199.8)</td>
<td>13.7 (0.8–117.6)‡</td>
</tr>
<tr>
<td>Serum apo B (mg/dl)*</td>
<td>148±35</td>
<td>100±23§</td>
</tr>
</tbody>
</table>

All values are mean±SD except those for age and alcohol consumption* (median and [range]) and for serum cholesterol, VLDL cholesterol, and serum Lp(a)† (geometric mean and [range]).

§p<0.001. All other differences are not significant.

Discussion

The findings of the present investigation strongly support the view that serum Lp(a) levels are raised in FH heterozygotes.14,16 Furthermore, we have demonstrated for the first time that this is not a consequence of the raised serum LDL concentration per se because a control population with similarly elevated LDL cholesterol levels due to other primary hyperlipoproteinemias did not have raised serum Lp(a) values. This finding suggests that the inherited LDL receptor defect in FH is important in the genesis of the increased serum Lp(a) concentration. This defect is not the cause of raised LDL levels in sporadic or polygenic hypercholesterolemia or in familial combined hyperlipidemia (which were the hyperlipidemias present in the control population). Support for our findings comes from numerous epidemiological studies in which only weak correlations between serum Lp(a) concentration and serum LDL cholesterol levels have generally been found,2–10,13 although individuals with LDL levels of magnitude similar to those in the present study would have been encountered only infrequently in these investigations.

The possibility exists that the expression of the FH gene is rendered more likely in individuals in whom the serum Lp(a) concentration is high from some other genetic cause. This might be the case, for example, if there were a greater tendency for the development of tendon xanthomata or CHD in FH heterozygotes with high Lp(a) levels, which would bring the condition to clinical attention. In our investigation we have studied the families of our FH probands, and by comparing affected and unaffected first-degree relatives, we sought to determine whether high levels of Lp(a) are inherited independent of the FH gene. Serum Lp(a) concentrations were a little higher in unaffected relatives than in our control populations, but this difference did not achieve statistical significance. The more striking finding was of significantly lower Lp(a) values in unaffected as opposed to affected first-degree relatives. Utermann and his colleagues15 have previously provided indirect evidence that this is unlikely to be
the major explanation for the raised Lp(a) in heterozygous FH. They determined the apo(a) genotype of each of their FH patients and found that the Lp(a) concentrations were higher than would be expected from the effect of the apo(a) genotype alone.

Even though not the major reason for high serum Lp(a) levels in FH, it would seem likely that clinically evident features of the FH syndrome such as CHD would have some tendency to be more penetrant in families with high Lp(a) levels for reasons other than the LDL receptor defect. Thus, an earlier study showed an increased prevalence of those genetic isoforms of apo(a) that are associated with high Lp(a) concentrations in FH patients with CHD compared with those without CHD. In our own study family membership continued to operate as an independent influence on serum Lp(a) concentration, as it does in the general population. However, it is clearly not the case that genetic effects unrelated to the FH gene defect can be the major explanation for the increase in Lp(a) in patients with FH because the presence of the gene still doubles the mean Lp(a) level even when family membership was controlled for, as in the present investigation. Family membership effects are nonetheless of great interest in view of the previously reported familial influence on the risk of CHD within the FH population.

The findings of the present investigation differ from the earlier two studies in one important respect. We did not demonstrate any association between Lp(a) level and clinically overt CHD in our patients with FH. Both Seed and her coworkers and Wiklund and colleagues have recently reported that Lp(a) concentrations are higher in FH heterozygotes who have developed CHD than in those who have not. In both studies the criteria for identifying patients with CHD were similar to those in the present investigation. In none was coronary angiography performed on asymptomatic patients for obvious ethical reasons, but severe coronary artery disease may exist without symptoms on the one hand; on the other, sometimes disease confined to only a small portion of the coronary tree may produce symptoms. The distinction between patients with and without CHD must necessarily, therefore, be somewhat imprecise and may vary considerably between studies. The present investigation and that of Seed et al employed similar criteria for the diagnosis of FH, whereas the method of identification of Wiklund and colleagues may have included some patients with polygenic hypercholesterolemia or familial combined hyperlipidemia because only 73% had tendon xanthomata. Such patients, as the present study shows, have lower serum Lp(a) levels. Because their risk of CHD is less, the effect of their classification within the FH population would be to exaggerate the tendency toward low Lp(a) values in the group without CHD. Neither Seed et al nor Wiklund et al matched their FH patients with CHD for age and sex with those without CHD, as we have done. In both those studies and ours age and gender apparently had no effect on the serum Lp(a) level, and thus age-and-sex matching is unlikely to explain the difference. However, all three investigations were cross sectional, and there is a high attrition rate in FH due to premature death, so only a prospective study can
truly establish the effect of age and gender on serum Lp(a) levels in FH. There can, however, be no doubt that age and gender are strong determinants of the presence of CHD.14,24 This was reflected in the difficulty we had in finding older control patients without CHD because most either had CHD or had died. Therefore, in our view the only definitive means of evaluating Lp(a) as a risk determinant for CHD in FH is by a prospective study.

The explanation for the raised Lp(a) concentration is as yet uncertain, but because the gene for the LDL receptor is on chromosome 19 and that for apo(a) is on chromosome 6,12,25 a metabolic rather than a genetic explanation is likely. Perhaps the LDL receptor defect may directly contribute to the high Lp(a) by decreasing its rate of clearance from the plasma compartment, as suggested by some studies26,27 but not by others.28 Alternatively or synergistically there might be increased secretion of Lp(a) in FH, as there is evidence from turnover studies for direct hepatic secretion of apo B in LDL in FH29,30 in this condition, and Lp(a) is an LDL-like apo B-containing particle that lacks a VLDL precursor and is thus presumably directly secreted.

We can conclude that serum Lp(a) concentrations are raised as a consequence of inheriting FH. Whatever the explanation, high Lp(a) values are so prevalent in FH that they may now be regarded as a clinical feature of the condition. This may have practical significance in the diagnosis of FH. When hypercholesterolemia is discovered in the absence of tendon xanthomata in either the patient or a relative, the diagnosis of FH must necessarily be insecure.22 Our data and those of previous studies indicate that the finding of a high Lp(a) level in these circumstances greatly increases the likelihood that the patient has FH and that it may thus be of diagnostic importance.

Higher serum Lp(a) is a well-established risk factor for CHD in the general population.2,4-6 Our study, in which we were careful to match for factors other than Lp(a), provided no direct evidence for the hypothesis that the coexistence of raised LDL and Lp(a) levels could explain the worse prognosis in FH compared with that of other hyperlipidemias. However, when the early attrition rate is high and asymptomatic coronary disease may be common, as in FH, case-control studies may be misleading, and prospective studies are required to test this hypothesis adequately.

Acknowledgments

We are most grateful to Sisters M. Brading and M. Ravenscroft, who worked on this project as research nurses at various stages.

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KEY WORDS • coronary heart disease • lipoprotein(a) • familial hypercholesterolemia
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doi: 10.1161/01.ATV.11.4.940

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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