Effect of Nicotinic acid/Laropiprant in the lipoprotein(a) concentration with regard to baseline lipoprotein(a) concentration and LPA genotype

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ABSTRACT

Background. Lipoprotein(a) [Lp(a)] is a lipoprotein in which apolipoproteinB-100 is linked to apolipoprotein(a) [apo(a)]. Significant variation in Lp(a) concentration is specific to LPA gene, which codes for apo(a). Nicotinic acid (NA) is used for treatment of dyslipidemias, and the lowering effect of NA on Lp(a) has been previously reported.

Objective. To evaluate the Lp(a) lowering effect of 1 g/20 mg and 2 g/40 mg day of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the LPA genotype.

Methods. In an open-label, 10-week study, 1 g/20 mg day of NA/Laropiprant for 4 weeks followed by 6 weeks of 2 g/40 mg day conducted at 3 centers in Spain, 82 subjects were enrolled. Patients were studied at baseline and at the end of both treatment periods and were enrolled in three groups: normal Lp(a) (<50 mg/dL), high Lp(a) (50–120 mg/dL) and very high Lp(a) (>120 mg/dL). The LPA genetic polymorphism was analyzed by a real-time PCR.

Results. There was a significant difference in LPA genotypes among Lp(a) concentration groups and an inverse and significant correlation between baseline Lp(a) concentration and LPA genotype was found (R = −0.372, p < 0.001). There were a significant decrease in total cholesterol, triglycerides, LDL cholesterol, apo B and Lp(a), and a significant increase in HDL cholesterol after NA/Laropiprant treatment, without changes in BMI. However, there were no statistical differences in percentage variation of analyzed variables depending on LPA genotype.

Conclusion. LPA genotype is a major determinant of Lp(a) baseline concentration. However, the lipid lowering effect of NA is not related to LPA genotype.

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Abbreviations: Lp(a), Lipoprotein(a); Apo(a), Apolipoprotein(a); LDL, Low density lipoprotein; LPA, apolipoprotein(a) gene; NA, Nicotinic acid; HDL, High density lipoprotein; PCR, Polymerase Chain Reaction; BMI, Body Mass Index; HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance; PCSK9, Proprotein Convertase Subtilisin/Kexin type 9; CETP, Cholesterol Ester Transfer Protein.

Clinical Trial registration number: NCT01321034.

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1. Introduction

Lipoprotein(a) [Lp(a)] is a type of lipoprotein particle found in human plasma, included in apoB-100 containing particles in which apolipoprotein B-100 is linked by a single disulfide bridge to a unique glycoprotein, apolipoprotein(a) [apo(a)] [1]. Except for apo(a), Lp(a) is essentially indistinguishable from low density lipoproteins (LDLs), both in structure and in its physical and chemical properties. Because of the presence of apo(a), Lp(a) and LDL are metabolically distinct and it is evident that the special characteristics of Lp(a), including its size and density heterogeneity, are almost entirely attributable to apo(a) [2]. Epidemiological studies have documented that high plasma Lp(a) concentrations are associated with a high risk of cardiovascular disease [3,4]. However, the mechanism of atherogenicity of Lp(a) is currently not known [5], but may include the vessels wall loading of cholesterol transported by Lp(a), a high risk for thrombosis by the inhibition of conversion of plasminogen to plasmin [6], and the transport of proinflammatory oxidized phospholipids [7].

Lp(a) is unique among lipoproteins in that its plasma concentrations varies from 0.1 to 300 mg/dL among individuals. Significant variation in plasma Lp(a) concentration is specific to the LPA gene locus (OMIM 152200), which codes for the apo(a) moiety of Lp(a) [8]. Several studies have confirmed that variation at the LPA gene on chromosome 6q26-27 accounts for most of the variability in plasma Lp(a) concentration [9,10]. This variation is partially due to the highly size heterogeneity of apo(a) that contains repeated domains that bear a high degree of homology to the plasminogen kringle IV sequence [11]. The kringle IV-like domains in apo(a) are divided in 10 types according to amino acid sequence. The kringle IV-2 sequence is present in a variable number of identically repeated copies (from 3 to > 60) and the number of kringle IV-2 repeats is inversely correlated with the Lp(a) concentration [4,12], but positively associated with the development of myocardial infarction, even after adjustment of Lp(a) concentration [4].

Nicotinic acid (NA) is a commonly used drug in the treatment of dyslipidemias because of its capacity to decrease LDL cholesterol and triglycerides and to increase HDL cholesterol [13]. In addition, the lowering effect of NA on Lp(a) concentration has been reported in different studies [14,15]. The Lp(a) reduction by niacin has been described to be highly heterogeneous, ranging between 10% and 40% arguing differences in patients selection, drug dose, length of drug administration, and methods for Lp(a) quantification [16]. However, the effect of baseline Lp(a) concentration and the Lp(a) size in the effect of niacin therapy has not been reported. This topic could be clinically important because the lowering effect of NA on Lp(a) seems to be related to apo(a) hepatic synthesis [15], which is very sensitive to apo(a) size [17].

For that reason, we hypothesized that the Lp(a) lowering effect of nicotinic acid could be dependent on the baseline pretreatment Lp(a) concentration, and that the Lp(a) size could be a major factor related to the variability of lowering effect of nicotinic acid. The aim of this study was to evaluate the Lp(a) lowering effect of 1 g/20 mg and 2 g/40 mg day of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the number of kringle IV-2 repeated copies of the LPA gene. We used NA/Laropiprant coadministration because Laropiprant is a selective antagonist of PGD2-receptor subtype-1 and reduces NA-induced flushing improving patient’s compliance to NA treatment [18], although this coadministration has been recently withdrawn from the market due to lack of cardiovascular benefit [19].

2. Material and methods

2.1. Study design

In an open-label, 10-week study, 1 g/20 mg day of NA/Laropiprant for 4 weeks followed by 6 additional weeks of 2 g/40 mg day conducted at 3 centers in Spain, we enrolled 82 subjects (ClinicalTrials.gov Identifier: NCT01321034). The consort diagram for the clinical trial is shown in Fig. 1. The trial was designed by two of the authors (AC and FC) who had full access to the data. NA/laropiprant was obtained from Merck, USA which had no role in the design or interpretation of the results of the study.

2.2. Subjects

Volunteers were selected from three Lipid Units in the Northeast of Spain. All volunteers before any study procedure gave written inform consent to a protocol previously approved for the Ethical Committees of our institutions.

The inclusion criteria were the following: age >18 and <80 years; LDL cholesterol between 70 and 190 mg/dL; triglycerides <500 mg/dL; at least 2 Lp(a) determinations previous to the beginning of the study without differences >20%; and no lipid lowering therapy or on stable doses in the last 3 months. Patients were homogeneously enrolled in three groups: normal Lp(a) (<50 mg/dL), high Lp(a) (50–120 mg/dL) and very high Lp(a) (>120 mg/dL). Exclusion criteria were: liver disease or liver enzymes >2 times higher than reference values; creatinine >2 mg/dL; active peptic ulcer; clinical gout in the last year; uncontrolled diabetes (HbA1c >8%); Lp(a) concentration <10 mg/dL, or enrolment in other drug clinical trial in the previous 3 months.

2.3. Study visits and biochemical determinations

Patients were studied at baseline and at the end of the two treatment periods (weeks 4 and 10). An adverse effects questionnaire and a physical examination were completed in each visit. Volunteers attended all study visits after, at least, 10 h of fasting, and the following parameters were determined in serum: total cholesterol, triglycerides, HDL-cholesterol, Lp(a), apolipoprotein AI and apolipoprotein B, and safety biochemical parameters: glucose, uric acid, creatinine, liver and muscle enzymes. All biochemical determinations were performed in a central laboratory as previously described [20]. The quantitative determination of Lp(a) in plasma was carried out by rate nephelometry, in an IMMAGE 800® Immunochromestry System (Beckman Coulter).

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2.4. Genetic analysis

The LPA genetic polymorphism responsible of the Lp(a) size variability was analyzed by a real-time PCR-based methodology [21]. Briefly, genomic DNA was extracted from peripheral leukocytes using established protocols. A multiplexed qPCR was carried out using TaqMan probes for LPA KIV2 (exon 4) and an endogenous single-copy control gene, RNase P. Thermocycler conditions were: 95 °C hot-start for 10 min, followed by 40 cycles of 95 °C for 15 s, 60 °C for 1 min.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 15.0 (Chicago, IL, USA) using a significance level of $P < 0.05$. Data are expressed as means $\pm$ standard deviation (SD) for continuous variables with normal distribution and medians (percentile 25–percentile 75) for variables with a skewed distribution. ANOVA and Kruskal–Wallis tests were performed for multiple independent variables comparison. Different doses of NA/laropiprant effects on study outcomes were evaluated by repeated measures ANOVA or the Friedman test, as appropriate. The study of the variables independently associated with variation in Lp(a) concentration after 2 g/40 mg of NA/Laropiprant was carried out using multiple linear regression introducing as independent variables: Gender, BMI, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, Apo B, Apo AI, baseline Lp(a) concentration and LPA genotype. Linear regression analysis was also performed to study the variation in Lp(a) plasma concentration explained by LPA genotype.

3. Results

Of the 82 subjects, 43 subjects were enrolled at Hospital Universitario Miguel Servet, 16 subjects at Hospital Royo Villanova, and 23 subjects at Hospital San Jorge. Ten subjects discontinued the study: 7 from Hospital Universitario Miguel Servet, 2 from Hospital Royo Villanova, and 1 from Hospital San Jorge. All discontinuations were due to skin side effects attributed to NA. Therefore, a total of 72 subjects completed all phases of the study and were included in the final analysis. In Table 1, anthropometric, clinic and lipid characteristics of studied subjects according to tertiles of Lp(a) concentration, are shown. There were no differences in any of analyzed lipid variables between the 3 groups of subjects according to Lp(a) concentration. The 3 groups were also homogeneous in relation to age, sex distribution, tobacco consumption and body mass index (BMI).

Table 1 – Anthropometric, clinic and lipid characteristics of studied subjects by groups of baseline Lp(a) plasma concentration.

<table>
<thead>
<tr>
<th></th>
<th>Normal Lp(a)</th>
<th>High Lp(a)</th>
<th>Very high Lp(a)</th>
<th>P a</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>0.054</td>
</tr>
<tr>
<td>Age, years</td>
<td>51.6 ± 13.2</td>
<td>45.9 ± 11.4</td>
<td>54.8 ± 13.2</td>
<td>0.945</td>
</tr>
<tr>
<td>Male, %</td>
<td>58.3</td>
<td>54.2</td>
<td>54.2</td>
<td>0.111</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>13.0</td>
<td>27.3</td>
<td>25.0</td>
<td>0.521</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 ± 4.7</td>
<td>25.8 ± 3.4</td>
<td>26.2 ± 3.3</td>
<td>0.652</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>230 ± 49.7</td>
<td>207 ± 28.9</td>
<td>211 ± 33.5</td>
<td>0.093</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>111 (90–206)</td>
<td>108 (70–159)</td>
<td>91 (75–152)</td>
<td>0.054</td>
</tr>
<tr>
<td>HDL-c, mg/dL</td>
<td>58 ± 18.1</td>
<td>59 ± 17.1</td>
<td>63 ± 17.4</td>
<td>0.266</td>
</tr>
<tr>
<td>LDL-c, mg/dL</td>
<td>140 ± 46.3</td>
<td>124 ± 23.9</td>
<td>123 ± 27.8</td>
<td>0.186</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>31.8 ± 17.6</td>
<td>90.6 ± 19.2</td>
<td>203 ± 57.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo AI, mg/dL</td>
<td>154 ± 30.6</td>
<td>160 ± 30.3</td>
<td>169 ± 25.5</td>
<td>0.299</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>102 ± 24.2</td>
<td>97.8 ± 18.2</td>
<td>95.5 ± 22.0</td>
<td>0.674</td>
</tr>
</tbody>
</table>

Lp(a), lipoprotein(a); BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B.

a ANOVA and Kruskal–Wallis tests were performed for multiple independent variables comparison.
The variation of lipid and anthropometric variables after 10 weeks of NA/Laropiprant treatment according baseline Lp(a) concentration groups is shown in Table 3. There were no statistical differences in percentage variation of any analyzed variable depending on baseline Lp(a) concentration. Although a trend towards higher Lp(a) and apo B concentrations decreases with higher baseline Lp(a) concentration was observed (−9.2% ± 3.7%, −20.7% ± 5.4%, −29.5% ± 2.2% for Lp(a) and −0.01% ± 5.4%, −5.0% ± 5.0%, −8.5% ± 4.6% for apo B), it was not statistically significant. Fig. 3 shows the percentage of Lp(a) variation after 10 weeks of NA/Laropiprant treatment according to Lp(a) baseline concentration.

Also, variation of lipid and anthropometric variables after 10 weeks of NA/Laropiprant treatment was analyzed according to LPA genotype. As shown in Table 4, there were no statistical differences in percentage variation of analyzed variables depending on LPA genotype quintiles. When analyzing by linear regression the factors influencing the variation in Lp(a) concentration after 2 g/40 mg of NA/Laropiprant, neither baseline Lp(a) concentration nor LPA genotype was found to be an important factor in determining the Lp(a) percentage decrease.

### 4. Discussion

The strong association between high Lp(a) and cardiovascular disease has led the European Atherosclerosis Society to establish a concentration < 50 mg/dl as a desirable Lp(a) in the population, and to recommend a reduction of plasma Lp(a) as a secondary priority after reduction in LDL and total cholesterol levels in patients with established cardiovascular disease or diabetes [22]. Although there are no therapeutic drugs that selectively target elevated Lp(a) [23], there are in the horizon potent new drugs, such as PCSK9 antibodies [24], apo B synthesis inhibitors [25] or cholesterol ester transfer protein (CETP) inhibitors [26], which markedly reduce Lp(a), but NA is at present time the drug of choice for the treatment of elevated Lp(a) [22,27]. Therefore, the identification of subjects that could benefit most of NA use is highly relevant.

We have evaluated, for the first time, the influence of Lp(a) concentration and apo(a) size, measured through LPA

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**Table 2** - Lipid concentrations at baseline and after 1 g and 2 g/day of Nicotinic Acid.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Nicotinic Acid, 1 g/day</th>
<th>Nicotinic Acid, 2 g/day</th>
<th>p *</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>214 ± 39.2</td>
<td>207 ± 40.6 (−2.84%)</td>
<td>202 ± 39.4 (−5.41%)</td>
<td>0.013</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>109 (74–175)</td>
<td>94 (74–143) (−3.84%)</td>
<td>80 (67–117) (−13.29%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>59 ± 17.0</td>
<td>65 ± 18.8 (+11.84%)</td>
<td>70 ± 19.3 (+19.65%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>128 ± 34.5</td>
<td>116 ± 33.8 (−8.59%)</td>
<td>107 ± 29.2 (−13.69%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>105 ± 79.0</td>
<td>89 ± 70.1 (−15.37%)</td>
<td>78 ± 57.2 (−23.05%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>98.6 ± 21.7</td>
<td>91.5 ± 22.6 (−6.64%)</td>
<td>93.8 ± 27.6 (−4.36%)</td>
<td>0.028</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 3.72</td>
<td>26.5 ± 3.76 (+0.0%)</td>
<td>26.4 ± 3.91 (−0.31%)</td>
<td>0.514</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>95.6 ± 12.4</td>
<td>100 ± 12.7 (+5.55%)</td>
<td>97.5 ± 13.7 (+2.36%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Insulin (mUI/L)</td>
<td>7.2 (4.8–10.5)</td>
<td>8.8 (6.9–12.4) (±22%)</td>
<td>10.0 (6.9–15.2) (±39%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.6 (1.1–2.6)</td>
<td>2.2 (1.6–3.4) (+37.5%)</td>
<td>2.3 (1.6–3.7) (+43.75%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Lp(a), lipoprotein(a); Apo B, apolipoprotein B; BMI, body mass index; HOMA-IR, Homeostasis Model of Assessment — Insulin Resistance. *Repeated measures ANOVA or the Friedman test were performed.
genotype, in the Lp(a) lowering effect of NA. As expected, our data show an inverse and significant correlation between baseline Lp(a) concentration and LPA KVI-2 genotype. This is in agreement with other studies that also found that the lower the number of LPA KVI-2 repetitions the higher the plasma Lp(a) concentration [4]. The mechanism of this inverse association is due to some LPA alleles producing intracellular very large protein products that are not secreted because they are retained in the endoplasmic reticulum [28]. Furthermore, the endoplasmic reticulum residence time of secreted apo(a) isoforms is determined by their size [28].

NA at a dose of more than 1.5 g/day decreases Lp(a) by approximately 20% [13], but with an important inter-individual variability [16]. In our work we demonstrate that this variability is not due to baseline Lp(a) concentration, or LPA KVI-2 variability. However, preliminary data presented recently by Artemeva et al. showed that in a small group of subjects, those with high molecular weight apo(a) isoforms determined by immunoblotting are more resistant to niacin treatment [29]. Our data would suggest that the effect of NA on Lp(a) is probably not related to the post-translational processing and secretion of apo(a) that are highly sensitive to apo(a) size [5,28]. Although the NA mechanism underlying Lp(a) reduction is not fully known, Chennamsetty et al. have recently demonstrated a reduction of hepatic APOA gene expression in transgenic mice and primary human hepatocyte cultures when treated with nicotinic acid [30]. This transcriptional LPA effect of NA would explain the lack of effect of apo(a) size found in our study.

As was expected, lipid profile of studied subjects was improved after treatment: total cholesterol, triglycerides, LDL cholesterol, apo B and Lp(a) were diminished, and HDL cholesterol was increased in expected range. However, a negative effect on glucose, insulin and HOMA-IR was also observed and it was also unrelated to the lipid lowering effect including Lp(a). Several studies have demonstrated that NA treatment is associated with hyperglycemia and insulin resistance, although the exact mechanisms responsible for this adverse effect of NA are not known [31]. NA causes a transient suppression of lipolysis followed by an increase in fatty acid release from adipose tissue. It would be possible that NA impairs insulin sensitivity by increasing plasma free fatty acids, which are delivered to muscle and liver and then

### Table 3 - Variation of lipid and anthropometric variables after 10 weeks of NA/laropiprant according to baseline Lp(a) groups.

<table>
<thead>
<tr>
<th>Normal Lp(a)</th>
<th>High Lp(a)</th>
<th>Very high Lp(a)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Δ % TC</td>
<td>−5.54 ± 3.62</td>
<td>−4.76 ± 3.39</td>
<td>−6.00 ± 2.30</td>
</tr>
<tr>
<td>Δ % TG</td>
<td>−16.34 ± 7.80</td>
<td>−10.79 ± 8.63</td>
<td>−12.97 ± 8.70</td>
</tr>
<tr>
<td>Δ % HDL-c</td>
<td>+18.0 ± 3.8</td>
<td>+22.0 ± 4.5</td>
<td>+18.8 ± 3.0</td>
</tr>
<tr>
<td>Δ % LDL-c</td>
<td>−14.5 ± 5.5</td>
<td>−12.9 ± 6.2</td>
<td>−13.9 ± 4.0</td>
</tr>
<tr>
<td>Δ % Apo B</td>
<td>−0.01 ± 5.4</td>
<td>−5.0 ± 5.0</td>
<td>−8.5 ± 4.6</td>
</tr>
<tr>
<td>Δ % BMI</td>
<td>−0.5 ± 0.7</td>
<td>−0.6 ± 0.5</td>
<td>+0.3 ± 0.5</td>
</tr>
<tr>
<td>Δ % Lp(a)</td>
<td>−19.2 ± 3.7</td>
<td>−20.7 ± 5.4</td>
<td>−29.5 ± 2.2</td>
</tr>
</tbody>
</table>

TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Apo B, apolipoprotein B; BMI, body mass index; Lp(a), lipoprotein(a).

* ANOVA test was performed for multiple independent variables comparison.

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generating fatty acid metabolites that reduce insulin signaling [32,33]. Recently, an animal model for niacin’s lowering of proatherogenic lipids and mechanisms of action relative to lipid metabolism has been developed, the high-fat high-fructose fed hamster. With the exception of HDL-C, the lipid effects of niacin treatment in the dyslipidemic hamster closely parallel those observed in humans. Moreover, the effects of niacin treatment on gene expression of hepatic proteins related to HDL metabolism were similar to those observed in human cells in culture. This animal model could serve to better understand the mechanisms responsible for the adverse effects of niacin in relation with hyperglycemia and insulin resistance [34].

There are several limitations to our study. First, we only studied white subjects, and therefore, our results may not apply to other ethnicities, since Lp(a) levels and its distribution differ between ethnic groups. Second, our method to determine LPA genotype reflects the sum of repeats on both alleles, and assumes an additive effect of both alleles on Lp(a) concentration. It would be possible that a more precise determination of LPA genotype with both alleles separately could add new information to our study.

The strength of this study is the novelty, as this is the first time that the Lp(a) lowering effect of Nicotinic acid/Laropiprant in subjects with different baseline Lp(a) concentrations and depending on the LPA genotype has been evaluated. However, a weakness is that the number of analyzed subjects is small, although enough for statistical power. Another weakness is the fact that the clinical use of Nicotinic acid/Laropiprant has been limited as it has been recently withdrawn from the market.

In conclusion, our work supports that LPA genotype is a major determinant of Lp(a) basal concentration. However, the lipid lowering effect of NA on the concentration of total cholesterol, LDL cholesterol, triglycerides and Lp(a) is not related to LPA genotype. There is a trend to higher reductions of Lp(a) concentration with NA in those subjects with very high levels of baseline plasma Lp(a). The translational potential of this paper is that although our results do not support the use of LPA genotyping in the clinical use of NA, LPA genotyping may still prove to be clinically useful in the use of niacin if patients with high Lp(a) levels or a given LPA genotype experience greater outcome benefits for a given niacin induced lipid effect.

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