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Statin therapy increases lipoprotein(a) levels

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Aims Lipoprotein(a) [Lp(a)] is elevated in 20–30% of people. This study aimed to assess the effect of statins on Lp(a) levels.

Methods and results This subject-level meta-analysis includes 5256 patients (1371 on placebo and 3885 on statin) from six randomized trials, three statin-vs.-placebo trials, and three statin-vs.-statin trials, with pre- and on-treatment (4–104 weeks) Lp(a) levels. Statins included atorvastatin 10 mg/day and 80 mg/day, pravastatin 40 mg/day, rosuvastatin 40 mg/day, and pitavastatin 2 mg/day. Lipoprotein(a) levels were measured with the same validated assay. The primary analysis of Lp(a) is based on the log-transformed data. In the statin-vs.-placebo pooled analysis, the ratio of geometric means [95% confidence interval (CI)] for statin to placebo is 1.11 (1.07–1.14) ($P < 0.0001$), with ratio >1 indicating a higher increase in Lp(a) from baseline in statin vs. placebo. The mean percent change from baseline ranged from 8.5% to 19.6% in the statin groups and -0.4% to -2.3% in the placebo groups. In the statin-vs.-statin pooled analysis, the ratio of geometric means (95% CI) for atorvastatin to pravastatin is 1.09 (1.05–1.14) ($P < 0.0001$). The mean percent change from baseline ranged from 11.6% to 20.4% in the pravastatin group and 18.7% to 24.2% in the atorvastatin group. Incubation of HepG2 hepatocytes with atorvastatin showed an increase in expression of *LPA* mRNA and apolipoprotein(a) protein.

Conclusion This meta-analysis reveals that statins significantly increase plasma Lp(a) levels. Elevations of Lp(a) post-statin therapy should be studied for effects on residual cardiovascular risk.

Keywords Lipoprotein(a) • Assay • Cardiovascular disease • Aortic stenosis

Introduction

Low-density lipoprotein (LDC)-targeted therapies are the mainstay of atherosclerotic cardiovascular risk reduction in both primary and secondary care populations due to their success in reducing cardiovascular events. Statin therapy is now used broadly, and according to the recent ACC/AHA guidelines,[1] 56 million Americans ages 40–75 years are eligible to receive a statin. Despite these benefits, significant residual risk remains in patients on statin therapy who participate in clinical trials, with more events occurring while patients are on statins than events prevented by statins. The aetiology of this residual risk is multifactorial but reflects the fact that statin therapy does not optimally treat all lipoproteins that are causal in atherogenesis, such as triglyceride-rich remnant lipoproteins and lipoprotein(a) [Lp(a)].

Lipoprotein(a) has been demonstrated to be a genetic, independent, and likely causal risk factor for cardiovascular disease (CVD).[2,3] The data for a causal association are strongest not only in primary care populations, but also in individuals already taking statins in high-risk primary and secondary settings, including those with persistently elevated low-density lipoprotein-cholesterol (LDL-C) levels,[4] those achieving LDL-C <70 mg/dL,[5,6] and those on statin therapy.[7]

One of the unresolved issues in Lp(a) biology is the effect of statin therapy on plasma Lp(a) levels.[2] Although the literature is mixed, it was noted as early as 1989 that lovastatin causes a dose-dependent increase in Lp(a).[8] A recent, small, study-level meta-analysis revealed a mean 11% increase in Lp(a) following statin therapy.[9] However, other studies have not shown a significant effect of statins on Lp(a). A limitation in interpreting this literature is the differences present in

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assay methodologies to measure Lp(a), the small size and heterogeneity of studies, the broad range of baseline Lp(a) levels that can vary 1000-fold requiring large datasets and the lack of individual-level patient data. To address these limitations, we performed an individual-participant-data analysis of six statin trials, using a single well-established Lp(a) method, to assess the change in Lp(a) following statin therapy.

Methods

Patient populations

The trials included in the current analysis were required to have pre-treatment and on-treatment, subject-level, Lp(a) levels, and the use of the same Lp(a) assay to minimize methodological differences and allow more robust interpretation of changes in Lp(a). The Lp(a) data in these trials have already been reported and include three statin-vs.-placebo trials (MIRACL,[10] children with familial hypercholesterolaemia,[11] and ASTRONOMER[12]) and three statin-vs.-statin trials (PROVE-IT,[13] REVERSAL,[14] and VISION[15]). The subject-level data in the placebo groups of these trials were combined for analysis, and the statin arms were also combined but also analysed individually. Statins utilized in the trials included atorvastatin 10 mg/day and 80 mg/day, pravastatin 40 mg/day, rosuvastatin 40 mg/day, and pitavastatin 2 mg/day. On-treatment Lp(a) levels were available at 4 weeks for PROVE-IT, 12 weeks for VISION, 16 weeks for MIRACL, 52 weeks for ASTRONOMER, 78 weeks for REVERSAL, and 104 weeks for children with familial hypercholesterolaemia.

Lipoprotein(a) assay methodology, cell culture, mRNA analysis, and statistical analysis methods are shown in the Supplementary material online, *Appendix*.

Results

Trial characteristics

The study included 5256 participants from six randomized statin trials (*Table 1*). The baseline characteristics of the trials were previously reported in detail.[11,12,15–17] In brief, MIRACL and PROVE-IT were conducted in participants following acute coronary syndromes, while the rest of the studies were performed in stable patients. The study also included children with familial hypercholesterolaemia, patients with stable coronary artery disease undergoing intravascular ultrasound (REVERSAL), patients with mild-moderate aortic stenosis (ASTRONOMER), and patients with hypercholesterolaemia (VISION).

Baseline and follow-up absolute lipoprotein(a) values in the placebo and statin groups

Table 2 displays the absolute baseline and follow-up median (interquartile range) Lp(a) values in the statin-vs.-placebo and statin-vs.-statin groups. Except for the ASRONOMER trial which had enrolled patients with aortic stenosis, the baseline median Lp(a) levels in the other trials was fairly similar.

Changes in log-transformed lipoprotein(a) values from baseline to follow-up in the placebo and statin groups

Due to skewness of the Lp(a) data, the primary analysis was based on the log-transformed data. The analyses of untransformed data are presented in Supplementary material online, *Table S2*.

In the statin-vs.-placebo trials directionality was noted in all three studies, with the statin arms of MIRACL and ASTRONOMER showing highly significant increases in Lp(a) compared to placebo ($P < 0.001$ for both). In the pooled analysis, the ratio of geometric means (back-transformed after log-transformation) [95% confidence interval (CI)] for statin to placebo is 1.11 (1.07–1.14) ($P < 0.0001$), with a ratio >1 indicating a greater increase in Lp(a) from baseline in the statin group than the placebo group. In the statin-vs.-statin trials similar directionality was noted in both statin arms of PROVE-IT and REVERSAL. In PROVE-IT, the atorvastatin arm had a significantly higher increase than the pravastatin arm ($P < 0.001$). In the pooled analysis the ratio of geometric means (back-transformed after log-transformation) (95% CI) for atorvastatin to pravastatin is 1.09 (1.05–1.14) ($P < 0.0001$).

Figure 1 displays the least means and CIs for changes in individual trials as well as dichotomized as placebo-vs.-statin and statin-vs.-statin trials.

Meta-analysis of the absolute changes in lipoprotein(a) in the placebo and statin groups

Table 3 displays the meta-analysis of the placebo-vs.-statin trials and the statin-vs.-statin trials in separate analysis using log-transformed data that were back-transformed to geometric means. In the pooled analysis of the placebo-vs.-statin trials, significantly greater increases in the ratio of the post-/pre-geometric means in Lp(a) were noted in the pooled-statin group vs. the pooled-placebo group, with directionality in all three trials and significance in the ASTRONOMER and MIRACL trials. In the pooled analysis of the statin-vs.-statin trials, the increases in the ratio of the post-/pre-geometric means in Lp(a) were statistically significant between the pooled atorvastatin vs. pooled pravastatin arms ($P < 0.0001$).

In the statin-vs.-placebo trials, the odds ratio (OR; 95% CI) of statin group to placebo group for the number of patients who had an increase in Lp(a) was 1.55 (1.33–1.80, $P < 0.0001$), with an OR >1 favouring the statin group to more likely to have an increase in Lp(a) than placebo. In the statin-vs.-statin trials (PROVE-IT and REVERSAL), the OR (95% CI) of atorvastatin 80 mg group to pravastatin 40 mg group for the number of patients who had an increase in Lp(a) was 1.16 (0.99–1.37, $P = 0.0681$), with an OR >1 favouring the atorvastatin 80 mg group to more likely to have an increase in Lp(a) than pravastatin 40 mg group.

Individual changes in lipoprotein(a) in the statin and placebo groups

Waterfall plots are presented displaying the entire range of changes in Lp(a) levels in both the placebo and statin groups (*Figure 2*). The graphs demonstrate significant heterogeneity in changes in Lp(a) in

Table 1 Baseline characteristics of the trials

Study	Number of patients	Interval between first and second Lp(a) level (weeks)	Number of patients (placebo)	Number of patients (statin)	Statin (dose)
Statin-vs.-placebo trials					
MIRACL	2237	16	1188	1149	Atorva (80 mg)
Children with FH	177	104	86	91	Prava (40 mg)
ASTRONOMER	194	52	97	97	Rosuva (40 mg)
Statin-vs.-statin trials					
PROVE-IT	2270	4	–	1150	Prava (40 mg)
				1115	Atorva (80 mg)
REVERSAL	250	78	–	111	Prava (40 mg)
				139	Atorva (80 mg)
VISION	42	12	–	21	Atorva (10 mg)
				21	Pitava (2 mg)
Total	5256				

FH, familial hypercholesterolaemia.

Table 2 Baseline and on-treatment absolute median (interquartile range) lipoprotein(a) values in the placebo and statin groups

Study	Placebo (n = 1371), Lp(a), median (IQR)		Statin (n = 3885), Lp(a), median (IQR)	
	Baseline	Follow-up	Baseline	Follow-up
Statin-vs.-placebo trials				
MIRACL	10.1 (5.0–28.3)	9.9 (4.6–31.1)	10.3 (4.9–28.2)	11.3 (5.0–33.3)
Children with FH	10.3 (4.3–23.1)	10.7 (4.2–24.3)	12.7 (6.1–29.4)	15.1 (6.2–35.2)
ASTRONOMER	27.0 (12.4–73.8)	27.9 (15.2–68.5)	29.9 (14.1–81.3)	35.0 (18.3–90.7)
Statin-vs.-statin trials				
REVERSAL			Prava 40	Prava 40
			8.9 (3.1–27.5)	9.5 (3.4–42.3)
			Atorva 80	Atorva 80
			6.1 (2.8–22.3)	6.9 (2.6–30.4)
PROVE-IT			Prava 40	Prava 40
			4.2 (2.1–23.5)	4.4 (2.1–28.6)
			Atorva 80	Atorva 80
			4.2 (2.1–20.6)	4.6 (2.1–40.8)
VISION			Atorva 10	Atorva 10
			14.4 (5.1–23.3)	11.3 (5.0–26.2)
			Pitava 2	Pitava 2
			10.6 (4.0–33.4)	6.7 (4.2–32.1)

FH, familial hypercholesterolaemia.

both groups, but overall the statin groups have a greater percentage of patients with an increase in Lp(a) levels compared with the placebo groups. About 720/1371 (52.5%) of placebo-treated patients had a decrease in Lp(a) vs. 1506/3885 (38.8%) statin-treated patients, and conversely 651/1371 (47.5%) of placebo-treated patients had an increase in Lp(a) vs. 2379/3885 (61.2%) of statin-treated patients. The absolute change in values in the placebo group ranged from -68.0 mg/dL to a maximum of +101.4 mg/dL, and in the statin group, ranged from -68.3 mg/dL to a maximum of +101.3 mg/dL.

Statin treatment increases *LPA* expression and apolipoprotein(a) production and secretion in HepG2 cells

The observation that statin therapy has an Lp(a)-raising effect is unexpected as statin therapy increases LDLR number on the surface of hepatocytes, which might be expected to increase Lp(a) clearance from the circulation. To gain insight into potential mechanism(s) whereby statin treatment might lead to increased Lp(a) levels, we

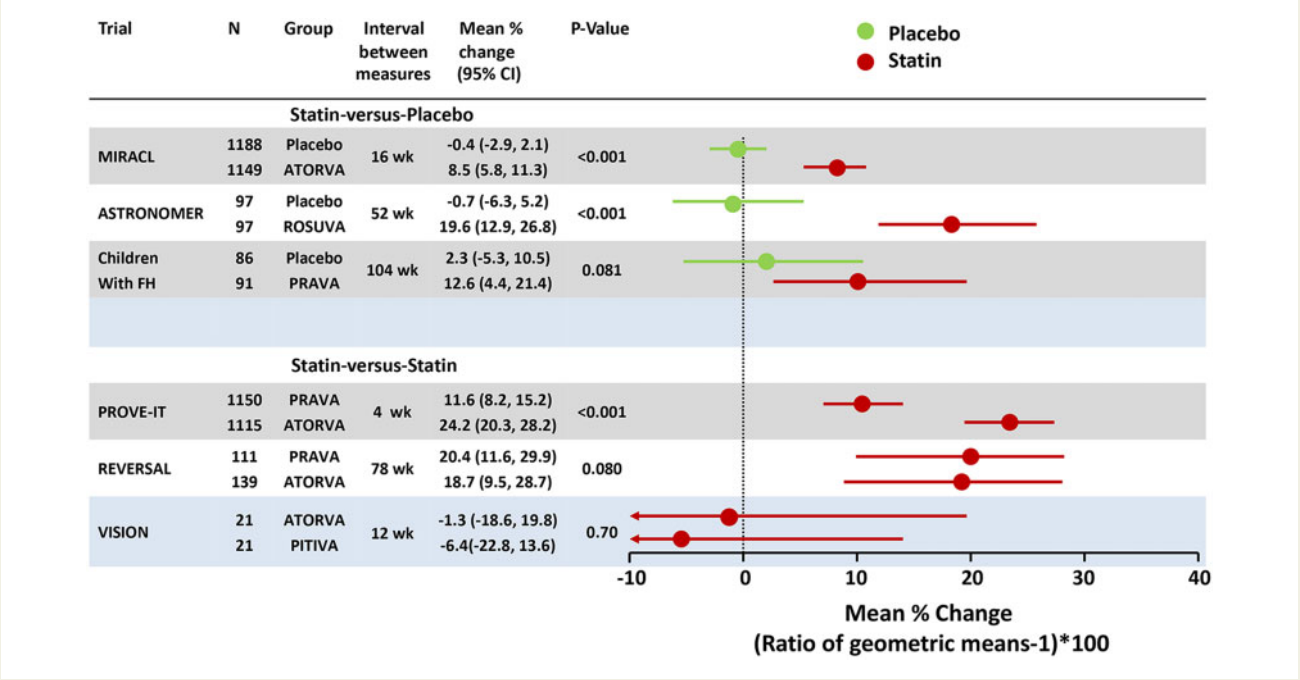


Figure 1 The Forest plot shows the mean percent changes (95% confidence interval) in lipoprotein(a) values in the placebo and statin groups in individual trials.

tested if statin treatment increased hepatic expression of *LPA mRNA* and thus Lp(a) assembly. We treated the human hepatoma cell line HepG2 with 5 or 10 μM atorvastatin for 24 h and evaluated expression of *LDLR*, *PCSK9*, and *LPA*. We treated the human hepatoma cell line HepG2 with 5 or 10 μM atorvastatin for 24 h and evaluated expression of *LDLR*, *PCSK9*, and *LPA*. As expected, atorvastatin treatment increased *LDLR* mRNA levels by 1.7-fold and *PCSK9* mRNA levels by 1.5-fold compared to the untreated cells (*Figure 3A* and *B*). The expression of *LPA* mRNA was 1.5-fold higher at 10 μM atorvastatin treatment (*Figure* 3C). Similar results were obtained using pravastatin treatment (Supplementary material online, *Figure*), except that pravastatin treatment significantly increased *LPA* mRNA levels at both 5 and 10 μM by 1.9- and 1.7-fold, respectively (Supplementary material online, *Figure S1C*). In a second study, HepG2 cells were treated with 10 μM atorvastatin for 12 and 24 h. Atorvastatin significantly increased *LDLR* expression in a time-dependent fashion by 1.6- and 1.9-fold as well as PCSK9 mRNA levels by two- and four-fold (*Figure* 3D *and E*). Atorvastatin induced a significant 1.5-fold increase in *LPA* expression compared to the untreated control ($t = 0$), but at a delay compared to *LDLR* and *PCSK9* expression. Finally, increasing doses of atorvastatin in significantly increased both the absolute amount of apolipoprotein(a) protein expression and secretion relative to cellular protein and the relative amount normalized to no atorvastatin treatment (*Figure* 4A–D).

Discussion

This individual-patient-data analysis demonstrates that Lp(a) levels increase significantly in patients started on statin therapy and that the findings were directionally consistent among most statins studied. Cell culture studies revealed a time and dose-dependent, statin-mediated increase in *LPA* mRNA expression and apolipoprotein(a) production, suggesting the mechanism is at least in part related to increased Lp(a) production. Whether statin-mediated increases in Lp(a) contribute to residual risk in patients treated with statin therapy should be evaluated in future studies. A pictorial summary of the data is shown in *Take home figure*.

Prior studies of changes in Lp(a) following statin therapy have been inconsistent, with most studies showing either a neutral effect or an Lp(a)-raising effect (reviewed in Ref.[9]). The ILLUMINATE trial most recently showed a dose-dependent increase of Lp(a) levels associated with atorvastatin during the run-in period, similar in extent to the current findings.[18] Because Lp(a) is not generally measured in clinical practice following initiation of statin therapy, this issue has not been widely appreciated.[9] It also follows that the effect of statins on Lp(a) metabolism has not been previously studied in experimental settings.

The metabolism of Lp(a) is not fully understood, particularly in how various pharmacological interventions affect plasma levels.[19] It is established that plasma Lp(a) levels are primarily genetically determined,[3] with the main determinant being production of apolipoprotein(a) by the *LPA* gene, and a smaller contribution from the *APOE* gene presumably via clearance mechanisms.[20] Although constitutive synthesis of apolipoprotein(a) is the primary determinant of Lp(a) levels, clearance mechanisms by various receptors, such as LDLR and LRP1, which can be further affected by apoE isoforms, CD36, SRB1, and plasminogen receptors, and additionally renal mechanisms play a role.[2,21] Plasma Lp(a) levels are inversely associated with smaller

Table 3 Analysis of log(post-treatment Lp(a) − log(pre-treatment Lp(a)) in the placebo and statin groups

Trial		Least squares mean (95% CI)—statin	Least squares means (95% CI)—placebo	Ratio of geometric means (95% CI) (statin/placebo, back-transformed)	*P*-value
Statin-to-placebo trials (ASTRONOMER, FH Children, and MIRACL)					
MIRACL	Ratio of geometric means (95% CI) (post/pre, back-transformed)[a]	1.09 (1.06–1.11)	1.00 (0.97–1.02)	1.09 (1.05–1.13)	<0.0001
ASTRONOMER	Ratio of geometric means (95% CI) (post/pre, back-transformed)	1.20 (1.13–1.27)	0.99 (0.94–1.05)	1.21 (1.11–1.31)	<0.0001
Children with FH	Ratio of geometric means (95% CI) (post/pre, back-transformed)	1.13 (1.04–1.21)	1.02 (0.95–1.10)	1.10 (0.99–1.23)	0.0806
Meta-analysis overall[b]	Ratio of geometric means (95% CI) (post/pre, back-transformed)			1.11 (1.07–1.14)	<0.0001
Trial		**Least squares mean (95% CI)—atorva 80 mg**	**Least squares means (95% CI)—prava 40 mg**	**Ratio of geometric means (95% CI) (atorva 80 mg/prava 40 mg, back-transformed)**	***P*-value**
Statin-to-statin trials (PROVE-IT and REVERSAL)					
PROVE-IT	Ratio of geometric means (95% CI) (post/pre, back-transformed)[a]	1.24 (1.20–1.28)	1.12 (1.08–1.15)	1.11 (1.06–1.16)	<0.0001
REVERSAL	Ratio of geometric means (95% CI) (post/pre, back-transformed)	1.19 (1.10–1.29)	1.20 (1.12–1.30)	0.99 (0.88–1.10)	0.8034
Meta-analysis overall[b]	Ratio of geometric means (95% CI) (post/pre, back-transformed)			1.09 (1.05–1.14)	<0.0001
Trial		**Least squares mean (95% CI)—atorva 10 mg**	**Least squares means (95% CI)—pitivastatin 2 mg**	**Ratio of geometric means (95% CI) (atorva 10 mg/pitivastatin 2 mg, back-transformed)**	***P*-value**
Statin-to-statin trial (VISION)					
VISION	Ratio of geometric means (95% CI) (post/pre, back-transformed)[a]	0.99 (0.81–1.20)	0.94 (0.77–1.14)	1.05 (0.80–1.39)	0.6987

FH, familial hypercholesterolaemia.
[a]The least squares mean of the log ratio for each treatment group, difference between treatment groups, the associated 95% CIs, and *P*-value in the individual study were estimated using an ANCOVA model with log(post-treatment Lp(a)/pre-treatment Lp(a)) as the dependent variable, treatment group as the fixed factor and natural log-transformed baseline Lp(a) levels as a covariate. The estimates obtained from model were converted back to the ratios in original scale.
[b]The estimates in the individual trial were pooled using the inverse variance weighting method and fixed effects model.

isoforms due to the ability of hepatocytes to synthesize a higher number of apolipoprotein(a) particles per unit time. Additional single nucleotide polymorphisms are also associated with Lp(a) levels,[22] but current evidence suggests that they co-segregate with smaller isoforms as the mechanism of higher plasma Lp(a).

Within these genetically mediated metabolic influences, additional factors may affect Lp(a) levels. For example, most steroid hormones suppress apolipoprotein(a) synthesis, while growth hormone increases Lp(a) levels. In contrast, in selected situations, Lp(a) acts as an acute phase reactant[23] and the *LPA* gene promoter contains an IL-6 response element. In fact, anti-IL-6 antibodies used in patients with rheumatoid arthritis may reduce Lp(a) levels ~30%, suggesting that inflammation associated with increased plasma IL-6 may increase Lp(a) levels.[24]

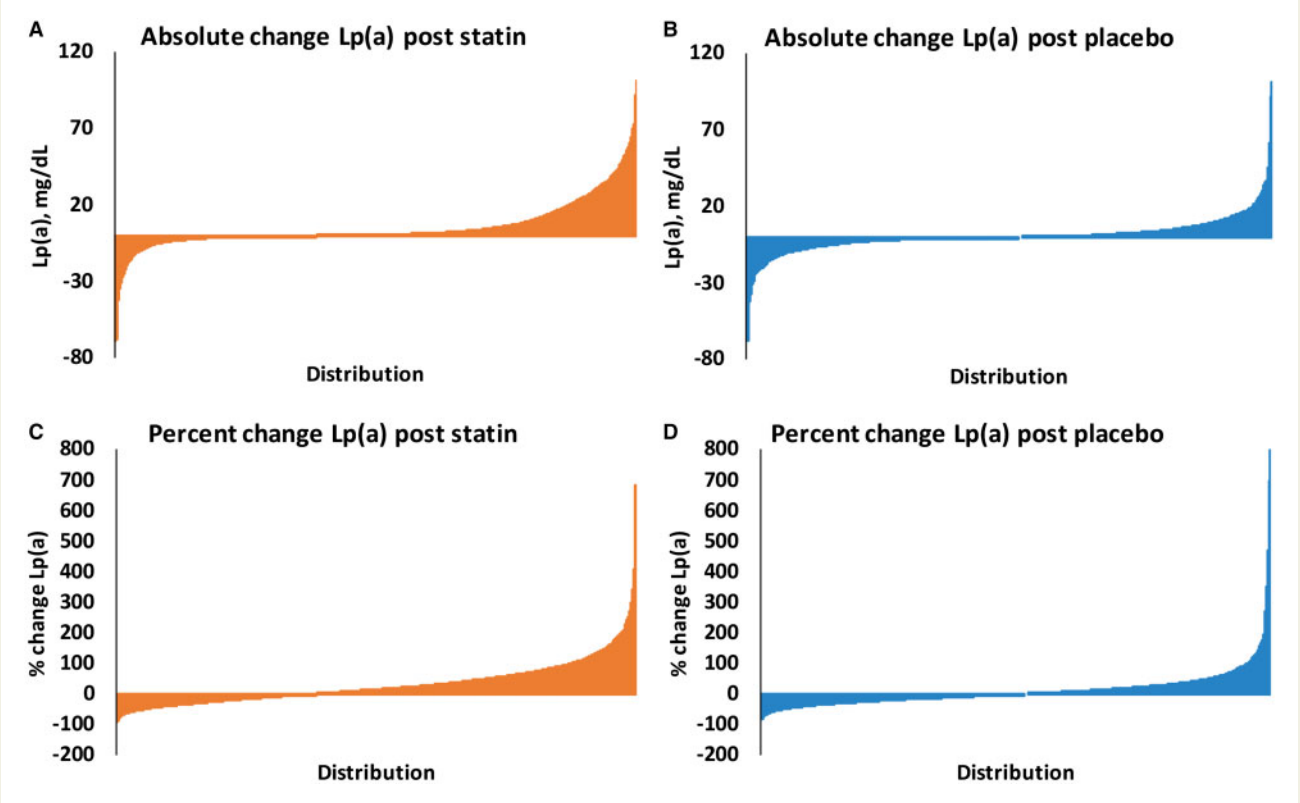


Figure 2 Waterfall plots of the absolute and percent change in lipoprotein(a) in the statin and placebo groups. (*A* and *B*) The absolute changes in lipoprotein(a) values in the statin and placebo groups are shown, respectively. (*C* and *D*) The percent changes in lipoprotein(a) values in the statin and placebo groups are shown, respectively.

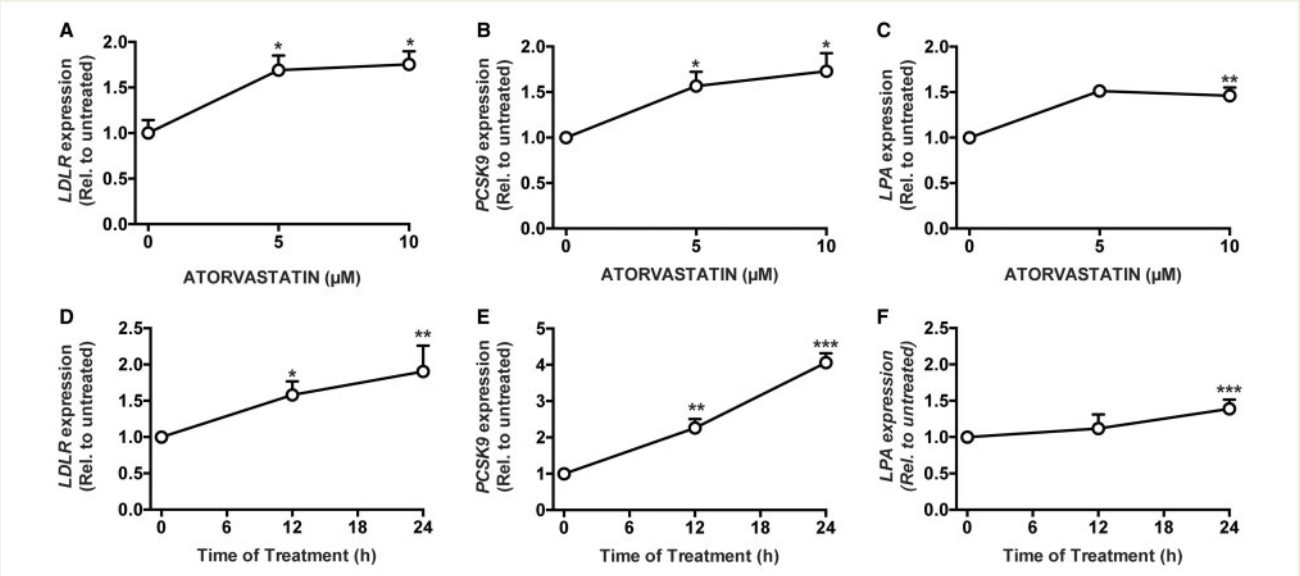


Figure 3 Atorvastatin treatment increases *LPA* expression in HepG2 cells. (*A–C*) HepG2 cells were incubated with increasing concentrations of atorvastatin. After a 24-h treatment mRNA expression of (*A*) *LDLR*, (*B*) *PCSK9*, and (*C*) *LPA* were measured ($n = 3–4$). (*D* and *E*) HepG2 cells were incubated for 12 and 24 h with 10-μM atorvastatin. After the indicated treatment times the mRNA expression of (*D*) *LDLR*, (*E*) *PCSK9*, and (*F*) *LPA* were measured ($n = 3–4$). Data are shown as mean ± standard deviation. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. untreated control.

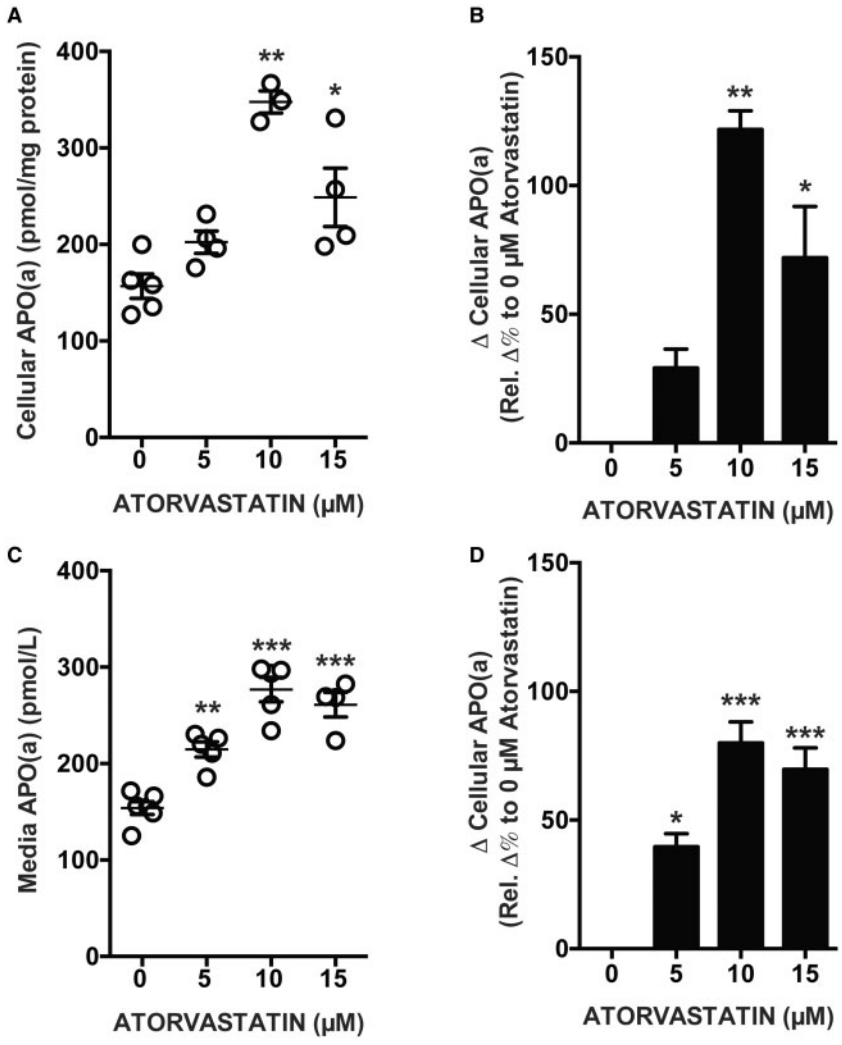


Figure 4 Atorvastatin increases apolipoprotein(a) protein production in HepG2 cells. HepG2 cells were incubated with increasing concentrations of atorvastatin. After a 24-h treatment (*A*) cellular apolipoprotein(a) protein levels were detected via ELISA and normalized for cell protein levels. (*B*) Relative increase (%) in cellular apolipoprotein(a) levels compared to untreated control (0 μM). (*C*) Secreted apolipoprotein(a) levels in media levels in were detected via ELISA and normalized for cell protein levels. (*D*) Relative increase (%) in media. Data are shown as mean ± standard deviation. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs. untreated control.

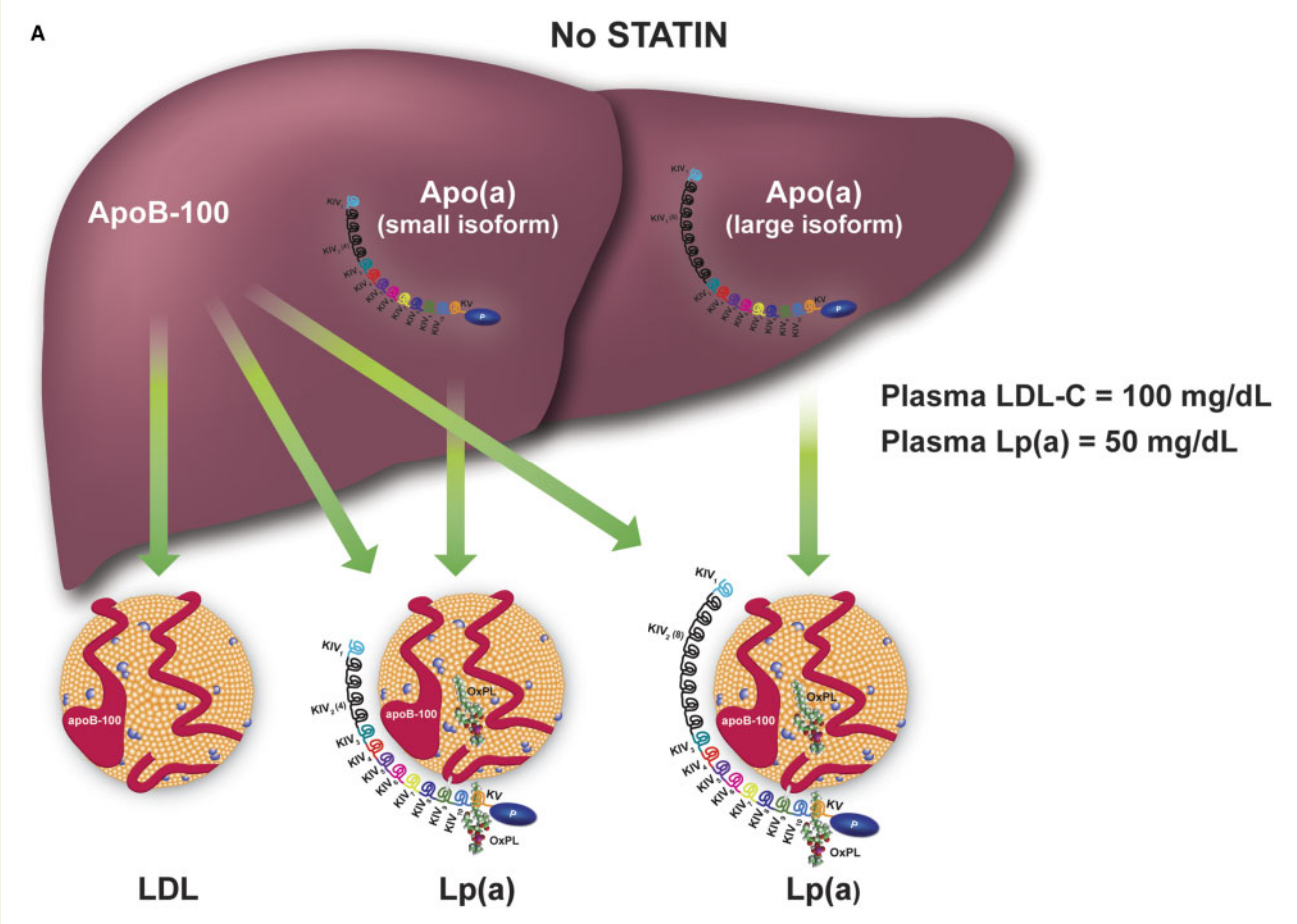
Niacin reduces Lp(a) levels 20–30% by inhibiting the *LPA* promoter.[6] In subjects with elevated Lp(a) (>50 mg/dL), PCSK9 inhibitors reduce Lp(a) levels by <15%.[25] Apheresis has a potent effect in acutely lowering Lp(a) and also has been shown to reduce events when patients are initiated on apheresis compared to events prior to therapy.[26] Antisense oligonucleotides targeting *LPA* mRNA potently reduce plasma Lp(a) levels by preventing apolipoprotein(a) synthesis.[27,28]

The underlying mechanisms by which statins affect Lp(a) levels are not fully defined. The current studies in HepG2 cells demonstrate that statins increase *LPA* mRNA and apolipoprotein(a) synthesis and secretion, suggesting that statin-induced increased production of apo(a) may lead to increased plasma levels of Lp(a) despite an increase in hepatic *LDLR* expression, for which Lp(a) has weak affinity. The rise in *LPA* mRNA was temporally later than *PCSK9* and *LDLR* mRNA expression, which may suggest a role of PCSK9 protein in up-regulating apolipoprotein(a) synthesis and secretion, as suggested recently.[29] Statins are also known to increase plasma PCSK9 protein levels, which may further potentiate Lp(a) production.

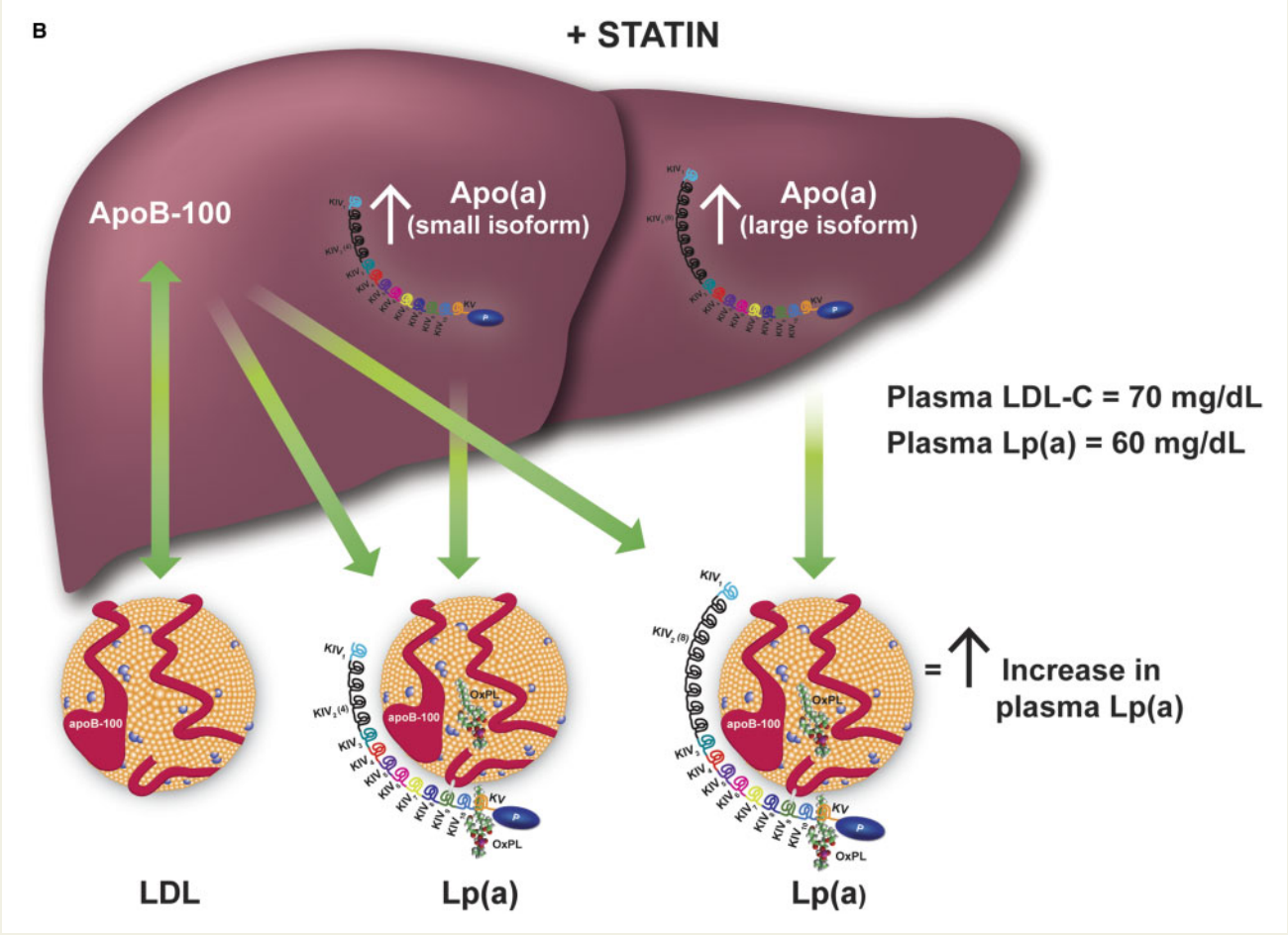
Despite the overall net increase in Lp(a) with statins, the data revealed a significant heterogeneity in changes in Lp(a) in both the placebo group and statin arms, but with a greater proportion of patients on statins having an increase, and importantly, a larger percentage increase. It has been recently noted in patients with serial blood samples enrolled in the placebo arms of apolipoprotein(a) antisense trials that a natural variability is present in Lp(a) levels, which can be manifested in occasional changes >25% from their predetermined baseline.[30]

There are several clinical implications to these findings. The first is that 'LDL-C' as currently measured not only includes LDL-C but

also Lp(a)-cholesterol (Lp(a)-C), irrespective of the method used. Thus 'LDL-C' is more accurately reflected as 'LDL-C + Lp(a)-C'.[31] The net result of statins is not only a lowering of LDL-C, but also an increase in Lp(a)-C via increase in Lp(a) mass. Thus, patients on statin therapy who have an elevated baseline Lp(a), and then have a further increase in Lp(a) due to statin therapy, will have a lower apparent LDL-C response to statin therapy, and may be labelled as 'statin resistant' or non-compliant. Second, patients with elevated Lp(a) may derive a less than optimal benefit of statins, as suggested by a recent meta-analysis of statin landmark trials.[7] Thus, in patients with elevated baseline Lp(a), surveillance of Lp(a) levels following statin therapy may be useful in understanding residual risk or recurrent events in such patients. The importance of elevated Lp(a) levels has also been recently highlighted in patients treated with PCSK9 inhibitors, showing that baseline elevated Lp(a) remains a strong risk factor even with significant LDL-C lowering.[32] Despite the increase of Lp(a) by statins, it is emphasized that statins benefit patients with elevated Lp(a) levels and it is recommended that such patients continue on statin therapy. The successful development of Lp(a)-specific therapies and demonstration that they reduce CVD risk in randomized outcome trials is required to fully address the impact of statin induced increases in Lp(a) on CVD risk. Limitations of this study include the fact that only three of the six trials had placebo groups, although they represent nearly 50% of the study. The study analysed studies available to the investigators' laboratory and may not represent all statin studies where Lp(a) was measured. The studies also had different extent of follow-up, which is both a strength and a weakness. More detailed studies with multiple timepoints are needed to ascertain the temporal changes and duration of effect. Additionally, LDL-C levels and other covariates were not consistently available to assess if the baseline LDL-C or if demographic characteristics and other biochemical factors may have influenced a change in Lp(a). Further studies will be needed to determine the relevance of the observations in HepG2 cells to Lp(a) synthesis in humans as well as to define whether additional mechanisms are at play behind these observations.



Take home figure The effect of statins on lipoprotein(a). (*A*) The liver output of low-density lipoprotei-like particles and lipoprotein(a) when no statin is present. The liver produces two isoforms of apo(a) which ultimately bind covalently to apoB-100 (site of this interaction is not fully elucidated) to create two different lipoprotein(a) particles. (*B*) Upon exposure of the hepatocyte to a statin, reduced hepatocyte cholesterol synthesis and uptake of circulating low-density lipoprotein particles results in a reduction in plasma low-density lipoprotein-cholesterol and apoB-100 particles. In conjunction, statin-induced increase in apolipoprotein(a) synthesis results in increased plasma lipoprotein(a), the mechanisms of which are not fully known currently.



Take home figure Continued

In conclusion, this well powered study shows significant increases in Lp(a) following statin therapy, as well as an increase in apolipoprotein(a) production in cell culture studies with statins. We propose that future studies evaluate this phenomenon and physicians consider measuring Lp(a) pre- and post-first initiation of statin therapy. The adverse consequences of increases in Lp(a) levels post-statin therapy may play a role in the residual risk in patients treated with statins and should be evaluated in future studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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