Impact of ezetimibe on plasma lipoprotein(a) concentrations as monotherapy or in combination with statins: a systematic review and meta-analysis of randomized controlled trials

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The aim of this meta-analysis of randomized placebo-controlled clinical trials was to assess the effect of ezetimibe on plasma lipoprotein(a) concentrations. Only randomized placebo-controlled trials investigating the impact of ezetimibe treatment on cholesterol lowering that include lipoprotein(a) measurement were searched in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases (from inception to February 26th, 2018). A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. A weighted random-effects meta-regression was performed to evaluate the impact of potential confounders on lipoprotein concentrations. This meta-analysis of data from 10 randomized placebo-controlled clinical trials (15 treatment arms) involving a total of 5188 (3020 ezetimibe and 2168 control) subjects showed that ezetimibe therapy had no effect on altering plasma Lp(a) concentrations (WMD: −2.59%, 95% CI: −8.26, 3.08, p = 0.370; I² = 88.71%, p(Q) < 0.001). In the subgroup analysis, no significant alteration in plasma Lp(a) levels was observed either in trials assessing the impact of monotherapy with ezetimibe versus placebo (WMD: −4.64%, 95% CI: −11.53, 2.25, p = 0.187; I² = 65.38%, p(Q) = 0.005) or in trials evaluating the impact of adding ezetimibe to a statin versus statin therapy alone (WMD: −1.04%, 95% CI: −6.34, 4.26, p = 0.700; I² = 58.51%, p(Q) = 0.025). The results of this meta-analysis suggest that ezetimibe treatment either alone or in combination with a statin does not affect plasma lipoprotein(a) levels.

Ezetimibe inhibits absorption of cholesterol at the brush border of the small intestine via the sterol transporter, Niemann–Pick C1-Like1 (NPC1L1)1. This leads to a decreased delivery of cholesterol to the liver, reduction of

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hepatic cholesterol stores and an increased clearance of cholesterol from the blood and studies have shown a reduction in LDL-cholesterol (LDL-C) by 17% when used alone and a reduction of 14–25% in combination with statins. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) in 18,144 subjects with recent acute coronary syndrome showed that ezetimibe 10 mg added to simvastatin 40 mg daily reduced LDL-C by 16% with a 6% reduction in the risk of the primary cardiovascular outcome.

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL)-like particle with proatherogenic, prothrombotic and proinflammatory properties that make it a significant contributor to atherothrombotic events. Lp(a) has been suggested to be an independent risk factor for cardiovascular disease with an increased odds ratio of 1.6; however, a large meta-analysis of 36 prospective studies showed the risk ratio was 1.13. Lp(a) is associated with acute coronary syndrome and increased levels are found commonly in patients with premature coronary heart disease. Therefore, therapeutic approaches capable of reducing elevated plasma Lp(a) concentrations may be important.

Kinetic studies have concluded that Lp(a) levels are mainly regulated by differences in biosynthesis, and biosynthetic changes have been associated to the Lp(a) lowering activity of anacetrapib. Recent reports have also indicated the role of plasminogen receptor KT in Lp(a) cell internalization, which is followed by recycling of the apo(a) component. Additional to these mechanisms, there is evidence showing that Lp(a) serves as an acute-phase reactant and its biosynthesis is augmented by inflammation. Ezetimibe is known to possess anti-inflammatory activity and may therefore affect Lp(a) production. The involvement of the LDL receptor (LDLR) in the catabolism and clearance of plasma Lp(a) has also been discussed. On the other hand, ezetimibe has been reported to potentiate the stimulating activity of statins on LDLR gene expression. Given these lines of evidence, it might be plausible that the benefits of ezetimibe in improving outcomes, such as that observed in the IMPROVE-IT study, may in part be due to a decrease in Lp(a) levels and this meta-analysis of all randomized controlled trials was undertaken to determine if ezetimibe therapy does decrease Lp(a) levels.

Methods

Search Strategy. This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms within titles and abstracts (also in combination with Mesh terms): (ezetimibe) AND (lipoprotein(a) OR lipoprotein (a) OR Lp(a) OR “Lp(a)”). Sensitivity of the search strategy was increased by using the wild-card term “*”. The search was limited to articles published in English language. The literature was searched from inception to February 26, 2018.

Study Selection. Original studies were included if they met the following inclusion criteria: (i) being a randomized placebo-controlled trial with either parallel or cross-over design, (ii) investigating the impact of ezetimibe vs placebo (or ezetimibe plus a statin vs statin alone) on plasma/serum concentrations of Lp(a), and, (iii) presentation of sufficient information on Lp(a) concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were: (i) non-randomized controlled trials, (ii) lack of a control group for ezetimibe treatment, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up Lp(a) concentrations.

Data extraction. Eligible studies were reviewed and the following data were abstracted: (1) first author’s name; (2) year of publication; (3) country was the study was performed; (4) study design; (5) number of participants in the ezetimibe and control groups; (6) medications including statins; (7) dose of ezetimibe; (8) treatment duration; (9) age, gender and body mass index (BMI) of study participants; (9) method of Lp(a) assay; and (10) data regarding baseline and follow-up plasma concentrations of Lp(a).

Quality assessment. Included studies were systematically evaluated for the risk of bias according to the Cochrane criteria, and as previously described, that included the assessment of each study for: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data) and selective outcome reporting. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

Quantitative Data Synthesis. Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) was used to undertake the meta-analysis. Effect size was calculated as: (measure at the end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at the end of follow-up in the control group – measure at baseline in the control group). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance weighting method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied. All values were collated as percentage changes. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [(SD pre-treatment)2 + (SD post-treatment)2 – (2 R × SD pre-treatment × SD post-treatment)], assuming a correlation coefficient (R) = 0.5. Heterogeneity index was assessed using I2 index and Cochrane Q test. If the outcome measures were reported in median and range (or 95% confidence interval), mean and standard SD values were estimated using the method described by Wan et al. Where standard error of the mean (SEM) was only reported, SEM was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). If the outcome measures were reported in median and range (or 95% CI), mean and SD values were estimated using the method described by Wan et al. In order to evaluate the influence of each study on the overall effect.
size, a sensitivity analysis was conducted using the leave-one-out method (i.e., removing one study each time and
repeating the analysis)35–38.

**Meta-regression.** As potential confounder of treatment response, baseline plasma Lp(a) levels were entered
into a random-effects meta-regression model to explore their association with the estimated effect size on plasma
Lp(a) concentrations37.

**Publication bias.** Evaluation of funnel plot, Begg’s rank correlation and Egger’s weighted regression tests
were employed to assess the presence of publication bias in the meta-analysis38. When there was an evidence of
funnel plot asymmetry, potentially missing studies were imputed using the “trim and fill” method39.

**Results**

**Characteristics of included studies.** A total of 408 clinical trials were identified of which 390 did not
meet the inclusion criteria and were excluded. Eighteen full-text articles were carefully reviewed for eligibility
from which 8 studies were excluded due to the lack of control group (n = 3), no ezetimibe arm (n = 2), Lp(a)
concentrations were not measured (n = 2), and not presenting numerical values (n = 1). After this assessment,
10 clinical trials were selected and included in this systematic review and meta-analysis. Flow chart that detailing
the studies identified, screened, those that were eligible and those that were included into the meta-analysis is
shown in Fig. 1.

Data were pooled from 10 clinical trials comprising a total of 5188 subjects, including 3020 and 2168 partic-
ipants in the ezetimibe therapy and control arms (individuals of the cross-over trials were considered in treat-
ment and control groups), respectively. Selected studies were published between 2002 and 2012. The range of
intervention periods was from 5 weeks40 to 12 weeks3,41–47. Study designs of included trials were parallel3,41–48
and cross-over group40. Evaluated studies enrolled subjects with primary hypercholesterolemia3,41–48 and severe
hypercholesterolemia40. Characteristics of the included clinical trials are shown in Table 1.

**Lp(a) assay methods.** The majority of the studies included in the meta-analysis quantified Lp(a) levels by
competitive enzyme-linked immunosorbent assay3,41–46,48, while other trials determined Lp(a) levels by a neph-
elometric assay (Dade Behring)40,47.

**Risk of bias in the included studies.** Several studies showed low risk of bias regarding random sequence
generation, only one trial had high risk of bias for this parameter38. Most of the included studies had a lack of
information about the allocation concealment, and a high risk of bias was found in one trial48. Several studies
presented insufficient information on the blinding process of the participants, study personnel and the outcome
assessors, and two trials showed high risk of bias47,48. Almost all of the assessed studies showed that there was a
low risk of bias for incomplete outcome data, only one trial exhibited limited information41. Finally, all selected
studies presented low risk of bias regarding selective outcome reporting. Cochrane guidelines applied to the
assessment of quality of bias in the studies that were included in the meta-analysis are shown in Table 2.
Effect of Ezetimibe on plasma Lp(a) concentrations. Overall, 10 studies comprising 15 treatment arms were included in the meta-analysis. Meta-analysis did not suggest a significant change in plasma Lp(a) concentrations following treatment with ezetimibe (WMD: −2.59%, 95% CI: −8.26, 3.08, p = 0.370; I² = 88.71%, p(q) < 0.001) (Fig. 2). The effect size was robust in sensitivity analysis (Fig. 2) and the effect size remained significant or marginally significant after omission of each single study from the meta-analysis.

In the subgroup analysis, no significant alteration in plasma Lp(a) levels was observed either in trials assessing the impact of monotherapy with ezetimibe versus placebo (WMD: −4.64%, 95% CI: −11.53, 2.25, p = 0.187;
\[ I^2 = 65.38\%, p_{(Q)} = 0.005 \] or in trials evaluating the impact of adding ezetimibe to a statin versus statin therapy alone (WMD: \(-1.04\%, 95\%\ CI: -6.34, 4.26, p = 0.700; I^2 = 58.51\%, p_{(Q)} = 0.025 \) (Fig. 3).

**Meta-regression.** To assess the impact of baseline Lp(a) concentrations on the effect of ezetimibe on plasma Lp(a) levels, a random-effects meta-regression was undertaken. The result did not suggest a significant association under a random-effects meta-regression model (slope: 0.135; 95\% CI: \(-0.504, 0.774; p = 0.679 \) (Fig. 4).

Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines. L, low risk of bias; H, high risk of bias; U, unclear risk of bias. Cochrane guidelines applied to the assessment of quality of bias in the studies that were included in the meta-analysis.

| Study            | Sequence generation | Allocation concealment | Blinding of participants, personnel and outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|------------------|---------------------|------------------------|----------------------------------------------------------|-------------------------|-----------------------------|----------------------|
| Ballantyne et al. | U                   | U                      | U                                                        | U                       | L                           | U                    |
| Davidson et al.   | L                   | U                      | U                                                        | L                       | L                           | U                    |
| Dojovne et al.    | L                   | L                      | U                                                        | L                       | L                           | U                    |
| Geiss et al.      | U                   | U                      | U                                                        | L                       | L                           | U                    |
| Goldberg et al.   | L                   | U                      | U                                                        | L                       | L                           | U                    |
| Kerzner et al.    | U                   | U                      | U                                                        | L                       | L                           | U                    |
| Knopp et al.      | L                   | U                      | U                                                        | L                       | L                           | U                    |
| Melani et al.     | L                   | U                      | U                                                        | L                       | L                           | U                    |
| Moutzouri et al.  | L                   | U                      | H                                                        | L                       | L                           | U                    |
| Saougos et al.    | H                   | H                      | H                                                        | L                       | L                           | U                    |

Figure 2. Weighted mean difference and 95\% confidence intervals for the impact of ezetimibe on plasma Lp(a) concentrations displayed as a Forest plot. The results of leave-one-out sensitivity analysis is shown in the lower panel.
Publication bias. Visual inspection of Begg's funnel plots showed an asymmetry in the meta-analyses of ezetimibe's effects on plasma Lp(a) concentrations. This asymmetry was corrected by imputing four potentially missing studies using "trim and fill" method, yielding a corrected effect size of $-5.56 \ (95\% \ CI: \ -10.50, \ -0.61)$ (Fig. 5). Consistently, Egger's regression test ($t = 3.38, \ df = 13, \ p = 0.005$) did suggest the presence of publication bias.
bias. However, there was no sign of publication bias according to the Begg's rank correlation test (tau = −0.27, z = 1.39, p = 0.166).

Discussion
In this meta-analysis of randomized placebo-controlled clinical trials, ezetimibe therapy was not related to a significant reduction of plasma Lp(a) levels. This result was robust in the sensitivity analysis and was confirmed both when ezetimibe was used as monotherapy and in combination with a statin. In a previous meta-analysis, ezetimibe monotherapy was found to cause a significant but small and not clinically relevant reduction (7%) in plasma Lp(a) levels. The present meta-analysis provides a more robust confirmation on the lack of any Lp(a)-lowering effect of ezetimibe compared with referenced meta-analysis because of including a larger number of randomized controlled trials (n = 10 vs. 7). Moreover, in addition to the impact of monotherapy, this meta-analysis also evaluated the impact of the combination of ezetimibe and statins (vs. statin monotherapy) on plasma Lp(a) levels that has not been the subject of any prior meta-analysis.

Lp(a) is associated with acute coronary syndrome and increased levels are found commonly in patients with premature coronary heart disease. Other studies including Lp(a) in a predictive model for cardiovascular prevention have suggested that the inclusion of Lp(a) in the models does increase their predictive value. However, whilst Lp(a) elevation is associated with cardiovascular disease it is still unclear if there is a benefit in lowering plasma Lp(a) levels specifically. Although no specific therapy for lowering Lp(a) is as yet approved, the body of evidence supports the reducing effects by lipoprotein apheresis, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, estrogen mimics and selective estrogen receptor modulators, nicotinic acid and some nutraceuticals. Moreover, selective apo(a) antisense therapy has shown promising lowering effects in patients with elevated Lp(a) in phase II trials. With this background, an additional pharmacological tool for Lp(a)-lowering would be desirable.

Ezetimibe has a modest LDL-C-lowering efficacy that has been associated with a significant improvement of cardiovascular prognosis in the IMPROVE-IT trial. Given the reduction in plasma LDL-C levels with ezetimibe and the similarity in the lipid composition between Lp(a) and LDL particles, it might be hypothesized that ezetimibe would have also an impact on plasma Lp(a) levels. However, this meta-analysis collecting the inconsistent results of 10 randomized placebo-controlled trials was convincing that this is not the case, despite few studies reported a beneficial effect of ezetimibe on plasma Lp(a) levels. Clear reasons explaining the divergent results of the included trials did not emerge from the analytical comparison of each of them; however, we cannot rule out the hypothesis that untested or unreported data might have contributed to such an inconsistency. Thus, for instance, whether baseline BMI might have affected the Lp(a)-lowering efficacy of ezetimibe cannot be excluded; accordingly, in 3 out of 4 trials reporting a significant impact of ezetimibe on Lp(a), average BMI was almost 29, whereas it was 26 in the only 2 trials reporting the baseline BMI value of the study participants and which also showed a neutral effect of ezetimibe on Lp(a). Hence, further trials with complete reporting of the baseline characteristics of the study subjects are warranted.

This meta-analysis has a number of limitations. Firstly, effects of ezetimibe therapy on Lp(a) were not the primary aim of the clinical trials and the studies were not powered for this. Secondly, there were only 10 trials available to be analysed giving a modest though robust number of subjects to undertake the analysis. Thirdly, the longest duration of the trials exploring the Lp(a)-lowering effect of ezetimibe was 12 weeks, which might be too short to allow a greater impact on plasma Lp(a) levels. Finally, given the skewed distribution of Lp(a) values in the population, further clarification would benefit from pooled analyses of individual patient data.

Conclusion
The results of this meta-analysis suggest that ezetimibe treatment does not reduce plasma lipoprotein(a) levels and therefore Lp(a) reduction does not contribute to its therapeutic effect in cardiovascular prevention.

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