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SYSTEMATIC REVIEW

Effect of Ezetimibe Monotherapy on Plasma Lipoprotein(a) Concentrations in Patients with Primary Hypercholesterolemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and Aims Ezetimibe reduces plasma low-density lipoprotein cholesterol (LDL-C) levels by up to 20%. However, its effect on plasma lipoprotein(a) [Lp(a)] concentrations in patients with primary hypercholesterolemia has not been defined.

Objective Therefore, we performed a systematic review and meta-analysis to assess this effect based on the available randomized controlled trials (RCTs).

Methods We searched the PubMed and SCOPUS databases from inception until 28 February 2017 to identify RCTs that investigated the effect of ezetimibe monotherapy on plasma Lp(a) concentrations in patients with primary hypercholesterolemia. We pooled mean percentage changes in plasma Lp(a) concentrations as a mean difference (MD) with a 95% confidence interval (CI).

Results Seven RCTs with 2337 patients met the selection criteria and were included in the analysis. Overall pooled analysis suggested that ezetimibe 10 mg significantly reduced plasma Lp(a) concentrations in patients with primary hypercholesterolemia by -7.06% (95% CI -11.95 to -2.18; $p = 0.005$) compared with placebo. No significant heterogeneity was observed ($\chi^2 = 5.34$; $p = 0.5$). Excluding one study from the analysis resulted in insignificant differences between the two groups ($p = 0.2$). Meta-regression did not find a significant association between the mean percentage changes in Lp(a) and other potential moderator variables, which included the mean percentage changes of LDL-C concentrations ($p = 0.06$) and baseline Lp(a) mean values ($p = 0.46$).

Conclusions Ezetimibe monotherapy (10 mg/day) showed a small (7.06%) but statistically significant reduction in the plasma levels of Lp(a) in patients with primary hypercholesterolemia. According to current literature, this magnitude of reduction seems to have no clinical relevance. However, further studies are warranted to clarify the mechanism mediating this effect of ezetimibe and to investigate its efficacy in combination with other drugs that have shown promise in lowering Lp(a) levels.

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Key Points

The effect of ezetimibe on plasma lipoprotein(a) [Lp(a)] levels has not been defined.

Ezetimibe 10 mg/day showed a statistically significant reduction in the plasma levels of Lp(a).

According to current literature, this reduction (7.06%) seems to have no clinical relevance.

Future studies are warranted to clarify the mechanism of this effect of ezetimibe and explore its use in combination with other Lp(a)-lowering drugs.

1 Introduction

In 1963, Kåre Berg described lipoprotein(a) [Lp(a)] as a distinctive lipoprotein with atherogenic and thrombotic characteristics [1]. Lp(a) is composed of a lipid core similar to that of low-density lipoprotein (LDL), including apolipoprotein B_{100} ($apoB_{100}$), which is bound by a covalent disulfide bond to apo(a), a glycoprotein [2–4]. Apo(a) has a structural similarity with plasminogen, a fibrinolytic proenzyme [5]. This similarity was defined as containing 3–40 plasminogen-like kringle IV domains repeated along the apo(a) structure [5–7]. The structural resemblance of Lp(a) to LDL and plasminogen is a possible explanation for its atherothrombotic properties [8]. However, the exact pathological actions of Lp(a) are not completely understood [2, 9]. Plasma Lp(a) levels are highly heritable and differ widely (over 1000-fold) among individuals [10] depending on variations in *LPA* gene sites responsible for apo(a) encoding [11, 12]. More than 100 variations have been identified in the *LPA* gene, and an inverse correlation is present between the number of repeated kringle IV type 2 and circulating Lp(a) levels [10, 13].

Lp(a) is considered an independent predictor for cardiovascular disease (CVD) [14, 15]. Lp(a) plasma levels > 30 mg/dL are considered raised [16, 17]. Recent Mendelian randomization studies revealed that elevated Lp(a) is a causal risk factor for atherosclerosis, myocardial infarction (MI), aortic valve stenosis, and stroke [14, 18]. In addition, Lp(a) levels > 30 mg/dL have been independently associated with a threefold elevation in the risk of major adverse cardiovascular (CV) events after coronary artery bypass grafting [19]. Lp(a) has also been associated with non-cardiac vascular diseases (e.g., abdominal aortic aneurysms) and other diseases (e.g., metabolic syndrome and chronic kidney disease) that are characterized by CV risk [20–23]. Therefore, several options have been proposed to decrease elevated Lp(a) levels, including lipoprotein apheresis (by up to 70%), niacin (by ~ 20%), mipomersen (by 25%), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (by up to 30%) [24–27]. Anacetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, also showed a lowering effect, ranging from 20 to 30%, on Lp(a) levels in a recent trial [28]. The antisense oligonucleotide [IONIS-$APO(a)_{Rx}$], which is still under evaluation, was associated with an approximately 80% fall in Lp(a) levels in a phase II trial [29].

Ezetimibe inhibits cholesterol absorption by binding to the intestinal cholesterol transporter Niemann-Pick C1 Like 1 (NPC1L1) [30, 31]. Ezetimibe monotherapy has been associated with an up to 20% reduction in plasma LDL cholesterol (LDL-C) [32]. Ezetimibe has shown (direct and/or indirect) anti-inflammatory properties in some studies [33–36]. On the other hand, Lp(a) is an acute-phase reactant that can be increased by inflammation [37–40]. This suggests that ezetimibe may have a possible reducing effect on Lp(a) levels. In 2010, Nozue et al. [41] investigated the effect on Lp(a) plasma levels of ezetimibe as monotherapy and combined with 12 weeks of statin therapy in 50 patients with dyslipidemia. In this non-randomized prospective study, ezetimibe monotherapy was associated with a significant 29% decrease in plasma Lp(a) levels. Apart from this small study, evidence about the effect of ezetimibe on plasma Lp(a) concentrations in patients with hypercholesterolemia is unclear and remains to be defined. Therefore, we conducted a systematic review and meta-analysis to assess the evidence related to this effect from randomized controlled trials (RCTs).

2 Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines during the preparation of this meta-analysis (Supplementary Table 1) [42]. All steps were conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [43]. This meta-analysis was not prospectively registered. Given the study design, neither institutional review board (IRB) approval nor patient informed consent were needed or obtained.

2.1 Literature Search Strategy

We conducted an electronic literature search of PubMed and SCOPUS from inception until 28 February 2017 using "ezetimibe" as the single keyword to increase the sensitivity of the search. No restriction filters were used during

the search. Moreover, we manually searched the reference lists of the retrieved articles for any potentially relevant studies. No additional keywords [e.g., lipoprotein(a) or Lp(a)] were used during the search because Lp(a) was mostly investigated as a secondary outcome and therefore this keyword was unlikely to be mentioned in the title or the abstract. Thus, we had to use this highly sensitive strategy to avoid missing any relevant study. Duplicates were removed using Endnote X7 (Thompson Reuter, CA, USA), then two authors (KA and NK) independently screened the retrieved articles in two steps: (1) title/abstract screening and (2) full-text screening of the eligible abstracts according to our predefined inclusion and exclusion criteria. Disagreement was resolved with the opinion of a third author (MB).

2.2 Study Selection

We included original studies that met the following criteria: (1) randomized, placebo-controlled trial, (2) investigated the effect of ezetimibe monotherapy on plasma Lp(a) concentrations in patients with primary hypercholesterolemia (LDL-C $>$ 130 mg/dL [$>$ 3.36 mmol/L] and triglycerides [TG] $\leq$ 350 mg/dL [$\leq$ 3.95 mmol/L]), and (3) reported sufficient data (for the main pooling analysis) on plasma Lp(a) concentrations at baseline and after a follow-up period in both groups, or reported the net change scores in both groups.

We excluded non-randomized trials, observational studies, experimental studies, reviews, book chapters, and theses; studies for which the full text was not available or that included non-English content; and studies from which the data could not reliably be extracted (e.g., reported in a complex graph) or were insufficient for the main pooling analysis.

2.3 Data Extraction

Two independent authors (KA and NK) extracted the following data from the included studies: (1) first author's name, (2) year of publication, (3) study location, (4) study design, (5) ezetimibe dose, (6) treatment duration, (7) study population characteristics, and (8) concentrations of Lp(a) and LDL-C. Disagreements were resolved by a third reviewer (MB).

2.4 Quantitative Data Synthesis

Mean percentage changes in plasma Lp(a) concentrations in both groups were pooled as a mean difference (MD) with a 95% confidence interval (CI) in a meta-analysis model. Heterogeneity was assessed by visual inspection of the forest plots and measured using *I*-squared and Chi squared tests. We interpreted heterogeneity according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions,* in which an alpha level (for a Chi squared test) $<$ 0.1 is considered significant heterogeneity and the *I*-squared test is interpreted as follows: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity [43]. In the case of significant heterogeneity, the random-effect model was used; otherwise, the fixed-effect model was employed.

We conducted a leave-one-out sensitivity analysis to investigate the influence of each study on the overall pooled effect estimate, i.e., removing one study each time and repeating the analysis. RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK) was used to conduct these analyses.

2.5 Meta-Regression

We performed a fixed-effect meta-regression using the unrestricted maximum likelihood method to investigate the association between the mean percentage changes of Lp(a) and other potential moderator variables, including the mean percentage change of LDL-C concentrations, and baseline Lp(a) mean values. Comprehensive Meta-Analysis (CMA) version 2 (Biostat, NJ, USA) was used to conduct this analysis.

2.6 Quality Assessment

Two independent authors (KA and NK) used the Cochrane Collaboration tool to assess the risk of bias in the included RCTs [43]. This tool includes the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The authors' judgments were classified as "low risk," "high risk," or "unclear risk" of bias. Disagreements were resolved by a third reviewer (MB).

2.7 Publication Bias

We minimized publication bias by conducting a comprehensive literature search. However, we could not assess the presence of publication bias using Begg's funnel plot or Egger's test because, according to Cochrane recommendations, these methods are not reliable in meta-analyses that include fewer than ten studies [43, 44]. Therefore, we used visual inspection of Doi plot asymmetry, a more sensitive method, to assess the presence of publication bias instead of the previously mentioned methods [45]. MetaXL version 5.3 (www.epigear.com) was used to generate the Doi plot.

3 Results

3.1 Flow and Characteristics of Included Studies

Our search of the literature yielded 9857 articles. After duplicates were removed and the title/abstract and full text were screened, only seven RCTs [46–52] met our criteria and were included in the analysis (see Fig. 1 for the PRISMA flow diagram).

Our analysis included 2337 patients with primary hypercholesterolemia who were randomly allocated to ezetimibe monotherapy ($n = 1597$) or placebo ($n = 740$) after washout of previous lipid-modifying drug therapy. All studies used the same dose of ezetimibe (10 mg/day) for 12 weeks and measured Lp(a) concentrations using competitive enzyme-linked immunosorbent assay. All patients of the included RCTs followed the National Cholesterol Education Program (NCEP) Step I diet. All studies were conducted in the USA and published between 2002 and 2004. Demographic and baseline parameters of the included studies are shown in Table 1.

3.2 Quality of the Included Studies

According to the Cochrane Collaboration tool, the quality of included RCTs ranged from moderate to high. Supplementary Fig. 1 provides a summary of the quality assessment domains of the included studies.

3.3 Effect of Ezetimibe on Plasma Lipoprotein(a) [Lp(a)] Concentrations

Meta-analysis of seven RCTs suggested that ezetimibe 10 mg/day significantly reduced plasma Lp(a) concentrations in patients with primary hypercholesterolemia (−7.06% [95% CI −11.95 to −2.18]; $p = 0.005$; Fig. 2) compared with placebo. No significant heterogeneity was observed ($\chi^2 = 5.34$; $p = 0.5$). Leave-one-out sensitivity analysis suggested that the overall pooled analysis was sensitive to the study by Knopp et al. [51]; excluding this study from the analysis resulted in an insignificant difference between the two groups ($p = 0.2$; Supplementary Table 2).

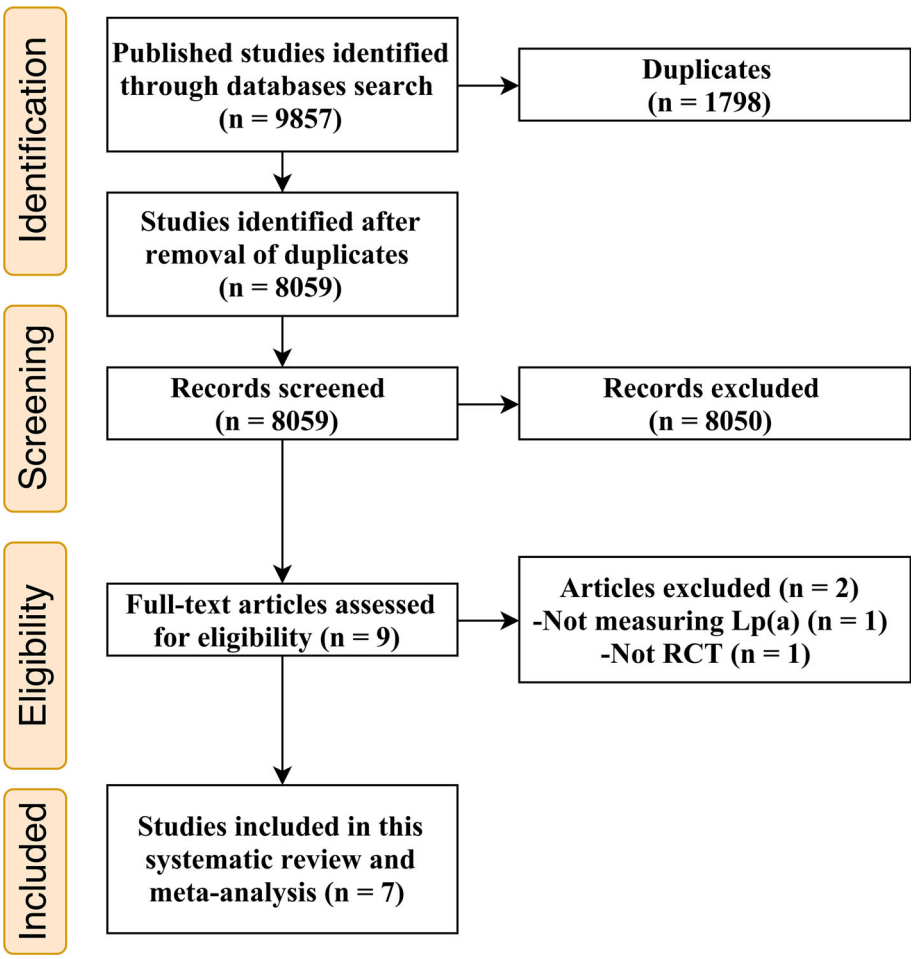

Fig. 1 PRISMA flow diagram of study screening and selection. *RCT* randomized controlled trial

Table 1 Demographic characteristics of the included studies

Study, country	Design [duration (wk)]	Population	Groups of interest	Age, y	Weight, kg	Sex, m/f	LDL-C[a]	Lp(a)[a]
Ballantyne et al. [46]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH [LDL-C 145–250 mg/dL (3.75–6.5 mmol/L); TG ≤ 350 mg/dL (3.95 mmol/L)]	EZE 10 mg ($n = 65$)	56.7 (11.7)[b]	NA	29/36	175.2 (2.7)[c]	NA
			PL ($n = 60$)	56.9 (12.1)[b]	NA	29/31	177.9 (2.7)[c]	NA
Davidson et al. [47]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH [LDL-C 145–250 mg/dL (3.75–6.5 mmol/L); TG ≤ 350 mg/dL (3.95 mmol/L)]	EZE 10 mg ($n = 61$)	60.3 (35–84)[d]	NA	24/37	181.3 (23.0)[b]	34.7[e]
			PL ($n = 70$)	58.8 (25–84)[d]	NA	31/39	177.4 (21.7)[b]	30.1[e]
Dujovne et al. [48]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH (LDL-C 130–250 mg/dL [3.36–6.5 mmol/L]; TG ≤ 350 mg/dL [3.95 mmol/L])	EZE 10 mg ($n = 666$)	57.9 (18–85)[d]	82.6 (45.5–158)[d]	332/334	167.8[e]	33.5[e]
			PL ($n = 226$)	58.1 (30–85)[d]	82.1 (43.2–146.3)[d]	102/124	168.0[e]	27.5[e]
Goldberg et al. [49]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH [LDL-C 145–250 mg/dL (3.75–6.5 mmol/L); TG ≤ 350 mg/dL (3.95 mmol/L)]	EZE 10 mg ($n = 92$)	NA	NA	35/57	176 (26)[b]	35 (30)[b]
			PL ($n = 93$)	NA	NA	38/55	174 (28)[b]	37 (38)[b]
Kerzner et al. [50]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH (LDL-C 145–250 mg/dL [3.75–6.5 mmol/L]; TG ≤ 350 mg/dL [3.95 mmol/L])	EZE 10 mg ($n = 72$)	55 (11)[b]	NA	31/41	177.9 (2.3)[c]	35 (4)[c]
			PL ($n = 64$)	58 (12)[b]	NA	24/40	177.9 (2.7)[c]	34 (4)[c]
Knopp et al. [51]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH [LDL-C 130–250 mg/dL (3.36–6.5 mmol/L); TG ≤ 350 mg/dL (3.95 mmol/L)]	EZE 10 mg ($n = 622$)	58.3 (20–86)[d]	83.3 (44.5–170.4)[d]	302/320	165.1[e]	30.8[e]
			PL ($n = 205$)	57.6 (24–79)[d]	84.0 (48.2–145.4)[d]	95/110	164.3[e]	33.6[e]
Melani et al. [52]; USA	RAN, DB, PC, PG (12)	Aged ≥ 18 y with PH [LDL-C 145–250 mg/dL (3.75–6.5 mmol/L); TG ≤ 350 mg/dL (3.95 mmol/L)]	EZE 10 mg ($n = 64$)	52.0 (26–75)[d]	NA	23/41	177.9 (23.2)[b]	30.8[e]
			PL ($n = 65$)	53.4 (32–76)[d]	NA	31/34	177.9 (19.3)[b]	33.6[e]

DB double-blind, *EZE* ezetimibe, *f* females, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *m* males, *NA* not available, *PC* placebo-controlled, *PG* parallel group, *PH* primary hypercholesterolemia, *PL* placebo, *RAN* randomized, *TG* triglycerides, *wk* week(s), *y* year

[a]LDL-C and Lp(a) are presented in mg/dL

[b]Data are presented as mean (standard deviation)

[c]Data are presented as mean (standard error)

[d]Data are presented as mean (range)

[e]Data are presented as mean only

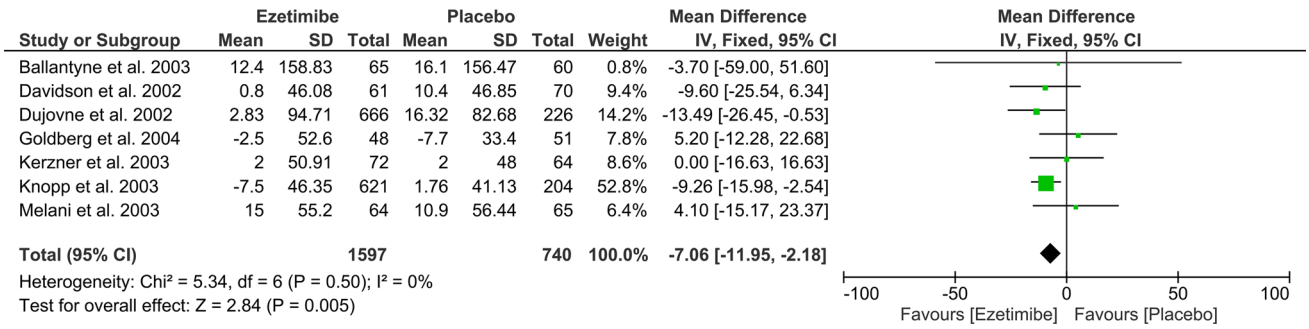

Fig. 2 Forest plot displaying the results of the meta-analysis of ezetimibe monotherapy effect on lipoprotein(a) concentrations in patients with primary hypercholesterolemia. *CI* confidence interval, *df* degrees of freedom, *IV* inverse variance, *SD* standard deviation

3.4 Meta-Regression

Fixed-effect meta-regression (on all included studies) did not suggest any significant association between the mean percentage changes of Lp(a) and that of LDL-C concentrations (slope: −3.19; 95% CI −6.52–0.14; $p = 0.06$; Fig. 3a).

The study by Ballantyne et al. [46] did not report the baseline Lp(a) value, which was considered a limitation for our meta-regression analysis needed to investigate the association between the mean percentage changes in Lp(a) and baseline Lp(a) values. We excluded this study from this analysis and conducted the analysis on the remaining six studies. However, this revealed an insignificant association (slope: 1.03; 95% CI −1.73–3.79; $p = 0.46$; Fig. 3b).

3.5 Publication Bias

The Doi plot was asymmetrical (quantitative measure, LFK index: 3.16, Supplementary Fig. 2), suggesting a potential publication bias in the studies reporting the impact of ezetimibe monotherapy on plasma Lp(a) concentrations in patients with primary hypercholesterolemia.

4 Discussion

The meta-analysis indicated that ezetimibe 10 mg/day lowers circulating Lp(a) levels by about 7%. This finding is of interest in the context of the mechanism(s) involved, vascular risk reduction, and potential additive/synergistic action with other drugs that may be prescribed together with ezetimibe.

An anti-inflammatory effect of ezetimibe may be involved in lowering circulating Lp(a) levels [41]. Also, the decrease in LDL-C and apoB, through the activation of LDL receptors, may be implicated in any small decrease in circulating Lp(a) levels observed in some, but not all, statin studies [53]. A similar mechanism may account for the effect of ezetimibe.

Any fall in Lp(a) levels after statin treatment may depend on the statin administered and when a sample was obtained; longer-term treatment with a statin may be more effective [53]. We could not evaluate the role of duration of treatment with ezetimibe because all the studies included in the present meta-analysis were for 12 weeks. Other studies report varying effects of ezetimibe on Lp(a) levels [41, 54–57], but these studies were excluded from the present meta-analysis because they compared baseline and post-treatment levels in the same patients (i.e., no placebo group). The effect on circulating Lp(a) levels ranged from a 25% ($p < 0.01$) decrease to non-significant change. Geiss et al. [57] investigated adding ezetimibe to patients undergoing apheresis but found no effect on Lp(a) levels. Heterogeneous patient characteristics, sample sizes, and treatment durations explains the variations in ezetimibe-related effects on Lp(a) levels among these studies.

It is difficult to estimate any risk reduction that can be attributed to a 7% lowering of circulating Lp(a) levels. In the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial, baseline on-study Lp(a) levels predicted CV events in both the

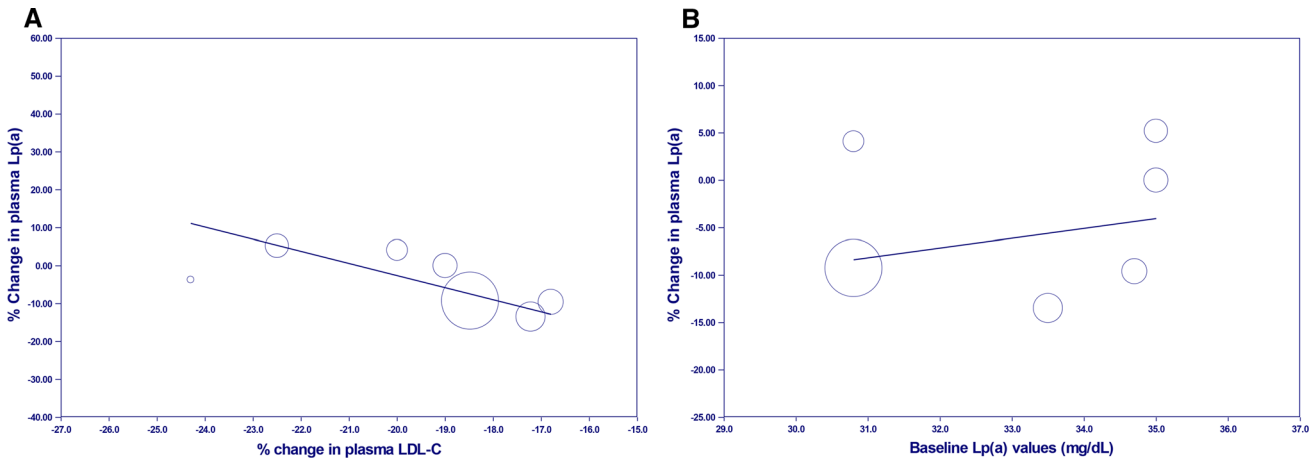

Fig. 3 **a** Meta-regression plot of the association between the mean percentage changes of lipoprotein(a) [Lp(a)] and the mean percentage changes of low-density lipoprotein cholesterol (LDL-C) concentrations after ezetimibe monotherapy 10 mg/day for 12 weeks in patients with primary hypercholesterolemia (number of studies = 7, slope −3.19; 95% confidence interval [CI] −6.52–0.14; $p = 0.06$); **b** meta-regression plot of the association between the mean percentage changes of Lp(a) and baseline Lp(a) values; after ezetimibe monotherapy 10 mg/day for 12 weeks in patients with primary hypercholesterolemia (number of studies = 6, slope 1.03; 95% CI −1.73–3.79; $p = 0.46$)

simvastatin + placebo and simvastatin + extended-release niacin 1500–2000 mg/day groups. Extended-release niacin decreased Lp(a) by 21% (i.e., a threefold greater decrease than reported in the present meta-analysis) but did not reduce CV events [58]. Therefore, the reported effect of ezetimibe in this meta-analysis could be considered clinically non-significant.

We found several studies investigating the combination of a statin and ezetimibe [46, 47, 49, 50, 52, 59–61]. Five of these [46, 47, 49, 50, 52] were included in this meta-analysis and included a combination arm comprising ezetimibe + a statin compared with ezetimibe or the same statin alone. None found a significant effect of the combination therapy on Lp(a) levels compared with statin monotherapy. However, Davidson et al. [47] found a significant lowering effect of ezetimibe + simvastatin on Lp(a) levels compared with ezetimibe monotherapy ($p = 0.03$). Another study in 70 patients with heterozygous familial hypercholesterolemia also found that ezetimibe added to their current statin had no effect on Lp(a) levels (up to 12 months of follow-up) [61]. Furthermore, in a similar study, 200 statin-intolerant patients with refractory familial hyperlipidemia received ezetimibe in addition to their maximal tolerated dose of statin [59]. A slight but insignificant increase in Lp(a) was observed after 3 months of the combination therapy. Another study in 72 patients at moderately high to high coronary heart disease risk observed an increase of 8 mg/dL in Lp(a) levels after 8 weeks of treatment with simvastatin + ezetimibe [60]. In an RCT, 591 patients with LDL-C levels 130–190 mg/dL (3.4–4.9 mmol/L) and TG levels 500 mg/dL were allocated to extended-release niacin (titrated up to 2 g), ezetimibe 10 mg + simvastatin 20 mg, or extended-release niacin + ezetimibe + simvastatin [62]. Ezetimibe + simvastatin and the triple combination group showed significant increases in Lp(a) levels from baseline after 24 weeks (% change = 23.1 and 2.7%, respectively; $p < 0.01$). On the other hand, niacin monotherapy significantly ($p < 0.01$) decreased Lp(a) levels by 12.4% from baseline after 24 weeks [62]. These studies do not suggest a major effect of ezetimibe on Lp(a) levels when added to a statin. However, the duration of treatment, statins used, and patient characteristics varied. A recent meta-analysis [63] concluded that statins slightly raise Lp(a) levels (weighted MD [WMD] 4.1 mg/dL; 95% CI 0.1–8.1; $p = 0.042$), but this analysis was sensitive to the exclusion of a study with rosuvastatin. This slight increase in Lp(a) with statins might diminish the possible moderate reduction of Lp(a) levels with ezetimibe [63].

Gaudet et al. [64] assessed the effect of alirocumab (a PCSK9 inhibitor) on Lp(a) levels through pooling data on 4915 patients with hypercholesterolemia from the phase III ODYSSEY program. Four comparisons were included in this analysis; two included ezetimibe as follows: (1) alirocumab (75/150 mg) versus ezetimibe plus statin, (2) alirocumab (75/150 mg) versus ezetimibe without statin [64]. After 12 weeks of treatment, the ezetimibe plus statin group showed a slight increase (by 1.5% from baseline) in Lp(a) levels, whereas a slight decrease was observed after 24 weeks (by 5.3% from baseline) [64]. These results are consistent with most of the previously mentioned studies that included ezetimibe combined with a statin. The ezetimibe without statin group experienced decreased Lp(a) levels, by 7.3 and 8.9% from baseline after 12 and 24 weeks, respectively; this is consistent with our results [64].

In a randomized partial-blinded trial, three groups of participants with LDL-C > 130 mg/dL (3.4 mmol/L) entered an initial 4-week run-in taking ezetimibe 10 mg, fenofibrate 160 mg, or ezetimibe placebo [65]. After the run-in period, alirocumab 150 mg every 4 weeks (days 1, 29, and 57) was added to the initial treatment regimens of the participants with LDL-C levels ≥ 100 mg/dL (2.5 mmol/L) ($n = 24$/group) [65]. Alirocumab + ezetimibe showed non-significant reductions in Lp(a) levels compared with alirocumab + placebo whether starting from the first day of the run-in period to day 71 (median % change: − 27, range − 71.4–35.8) or from the addition of the first dose of alirocumab to day 71 (median % change: − 9.2, range − 67–66.7) [65]. In this study, the mean free PCSK9 concentrations in the ezetimibe group became 24% (90% CI 4–47) higher than that in the placebo group before the addition of the first dose of alirocumab [65]. This effect may explain these results because it slightly increased the clearance of alirocumab in the ezetimibe group and subsequently diminished its lowering effect on Lp(a) levels [65]. However, the relatively small sample size in this study is an important limitation, and these results should be further investigated in larger RCTs. Furthermore, the combination of ezetimibe with other drugs that have shown promising results on lowering Lp(a) levels (e.g., mipomersen) should be assessed in large RCTs to investigate any additive/synergistic action between them and their effect on CV events, especially in high-risk patients with elevated Lp(a) levels.

This meta-analysis has some limitations. Most importantly, 26.7% of the meta-analysis population came from one study, and another study had 666 participants, which represents 28.5% of the meta-analysis population [48, 51]. This could explain the sensitivity of the results to the substantial weight of the study by Knopp et al. [51]. Moreover, all the included trials investigated the change in Lp(a) as a secondary outcome. These trials were conducted between 2002 and 2004, just after the US FDA approved the drug [66]. The main objective of these studies was to investigate and establish the efficacy and safety of this then

new drug as monotherapy or in combination with the standard treatment (statins). In all these studies, the primary outcome was the change in LDL-C levels. Furthermore, all studies were conducted in the USA for a duration of 12 weeks. Thus, we cannot comment on the effect of ethnicity and other treatment durations. On the other hand, the latter two characteristics ensure consistency. In this context, the same type of assay for Lp(a) was used in all studies.

5 Conclusion

Ezetimibe monotherapy 10 mg/day showed a small (7.06%) but statistically significant reduction in the plasma levels of Lp(a) in patients with primary hypercholesterolemia. According to current literature, this magnitude of reduction seems to have no clinical relevance. However, further studies are warranted to clarify the mechanism mediating this effect of ezetimibe and to investigate its efficacy in combination with other drugs that have shown promise in lowering Lp(a) levels.

Author Contributions KA contributed to the literature search, screening, data extraction, data analysis, and manuscript writing; DPM to the manuscript writing and revision; NK to the screening, data extraction, and manuscript writing; PM to the manuscript writing and revision; and MB to the study design, supervision, coordination and manuscript writing, and revision. All authors approved the final article.

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Compliance with Ethical Standards

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