Impact of alirocumab/evolocumab on lipoprotein (a) concentrations in patients with familial hypercholesterolaemia: a systematic review and meta-analysis of randomized controlled trials

Haibing Dai1,2*, Yonglin Zhu1,2*, Zuyi Chen1,2*, Rening Yan1,2, Jinsong Liu1,2, Ziyun He1,2, Lin Zhang3, Feng Zhang1,2, Shengkai Yan1

1Department of Laboratory Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China
2College of Laboratory Medicine, Zunyi Medical University, Zunyi, China
3School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
*These authors contributed equally to this work and should be considered co-first authors.

Abstract
Introduction: Familial hypercholesterolaemia (FH) is a common hereditary genetic disorder, characterized by elevated circulating low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] concentrations, leading to atherosclerotic cardiovascular disease (ASCVD). Two types of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors – alirocumab and evolocumab – are efficient drugs in the treatment of FH, which can effectively reduce Lp(a) levels.

Material and methods: Embase, MEDLINE, and PubMed up to November 2022 were searched for randomized clinical trials (RCTs) evaluating the effect of alirocumab/evolocumab and placebo treatment on plasma Lp(a) levels in FH. Statistics were analysed by Review Manager (RevMan 5.3) and Stata 15.1.

Results: Eleven RCTs involved a total of 2408 participants. Alirocumab/evolocumab showed a significant efficacy in reducing Lp(a) [weighted mean difference (WMD): –20.10%, 95% confidence interval (CI): –25.59% to –14.61%] compared with placebo. In the drug type subgroup analyses, although the efficacy of evolocumab was slightly low (WMD: –19.98%, 95% CI: –25.23% to –14.73%), there was no difference with alirocumab (WMD: –20.54%, 95% CI: –30.07% to –11.02%). In the treatment duration subgroup analyses, the efficacy of the 12-week duration group (WMD: –17.61%, 95% CI: –23.84% to –11.38%) was lower than in the group of ≥24 weeks’ duration (WMD: –22.81%, 95% CI: –31.56% to –14.07%). In the participants’ characteristics subgroup analyses, the results showed that no differential effect of alirocumab/evolocumab therapy on plasma Lp(a) concentrations was observed (heterozygous FH [HeFH] WMD: –20.07%, 95% CI: –26.07% to –14.08%; homozygous FH [HoFH] WMD: –20.04%, 95% CI: –36.31% to –3.77%). Evaluation of all-cause adverse events (AEs) between alirocumab/evolocumab groups and placebo groups [relative risk (RR): 1.05, 95% CI: 0.98–1.12] implied no obvious difference between the 2 groups.

Conclusions: Anti-PCSK9 drugs (alirocumab and evolocumab) may be effective as therapy for reducing serum Lp(a) levels in FH, and no differences were observed in treatment durations, participant characteristics, and other aspects of the 2 types of PCSK9 inhibitors. However, further experimental studies and RCTs are warranted to clarify the mechanism of PCSK9 inhibitors to lowering Lp(a) concentrations in FH. (Endokrynol Pol 2023; 74 (3): 234–242)

Key words: familial hypercholesterolaemia; lipoprotein (a); atherosclerotic cardiovascular disease; PCSK9 inhibitors; meta-analysis; randomized controlled trials

Introduction

Familial hypercholesterolaemia [FH, Online Mendelian Inheritance in Man (OMIM) #143890] is a common autosomal dominant disorder associated with elevated serum low-density lipoprotein-cholesterol (LDL-C) levels, which accelerates the development of premature coronary artery disease (CAD) in young adults if untreated [1, 2]. The most typical clinical phenotypic features of FH are xanthomas, xanthelasma, and corneal arcus, and it can lead to premature morbidity and mortality due to atherosclerotic cardiovascular disease (ASCVD) [3–5]. Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like particle synthesized by the liver, which is composed of a lipid core, including apolipoprotein B100 (apoB100), and associates with apo(a) through a covalent disulphide bond [6, 7]. It is a genetically predisposed lipoprotein, and compelling evidence shows that elevated plasma levels represent an independent risk factor.
factor for ASCVD in general [8]. Recent studies show that 30–50% of heterozygous FH (HeFH) have elevated Lp(a) levels and an increased risk of ASCVD [9,10], and could explain 5–20% of suspected FH, especially those with negative mutations in FH-related genes [11]. The correlation between the genetic prediction of Lp(a) and ASCVD risk was linear with the change of Lp(a) levels [12]. An analysis from the UK Biobank provided the largest study to date examining the risk of ASCVD associated with Lp(a), where the standardized risk of ASCVD was 11% higher for every 50 nmol/L increase [13]. Madsen et al. [14], based on a population study, found that a reduction of 50 mg/dL of Lp(a) over 5 years could reduce cardiovascular diseases (CVD) by 20% in the context of secondary prevention. Based on these data, the European Atherosclerosis Society recommended controlling Lp(a) concentrations below 50 mg/dL [15] and Lp(a) levels of 50 mg/dL or higher at baseline, after which the risk of ASCVD increased by 31% and 43%, relatively [16].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine pre-protein invertease mainly secreted by liver; it is an important regulator of hepatic LDL receptor (LDLR) [17]. PCSK9 could combine with LDLR in the recycling process and decompose in the cell, resulting in decreased LDLR and elevated plasma LDL-C levels. PCSK9 inhibitors can be divided into those inhibiting the binding of PCSK9 to LDLR, and those inhibiting the expression or interfering with the secretion of PCSK9. PCSK9 monoclonal antibodies, alirocumab and evolocumab, were approved to treat FH in 2015 by the US Food and Drug Administration (FDA) [18]; however, the relationship between PCSK9 inhibitors and Lp(a) levels has not been fully studied [19]. Some studies indicated that evolocumab significantly reduces Lp(a) levels, more effectively than LDL-C plasmapheresis [20]; alirocumab reduced Lp(a) through an alternative pathway in addition to LDL-C reduction [21]; the ODYSSEY OUTCOMES demonstrated that Lp(a) predicted total cardiovascular event risk, and relative and absolute risk reduction in the placebo and alirocumab group [22]; while another showed no difference in circulating Lp(a) levels after 24 weeks of adalimumab or ezetimibe treatment [23]. In view of the lack of comprehensive and quantitative evaluations about the efficacy, we conducted this meta-analysis including all randomized controlled trials (RCTs) published until November 2022 to further explore the efficacy of alirocumab/evolocumab on Lp(a) levels.

Material and methods

This study was reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [24], and it was registered in the PROSPERO international prospective register of systematic reviews (CRD42021279966).

**Literature search**

We included double-blind randomized-controlled trials (RCTs) assessing lipid changes by medication directed against alirocumab and/or evolocumab in patients with a clinical and/or genetic diagnosis of FH. Relevant studies on Embase, MEDLINE, and PubMed were searched from inception until 30 November 2022, restricted to RCTs, but without any language restrictions. Both medical subject heading (MeSH) terms and keywords, including “‘alirocumab’ [Supplementary Concept], “SAR236553”, “SAR-236553”, “REGN-727”, “monoclonal antibody REGN727”, “REGN727 monoclonal antibody”, “REGN727”, praluent”, “(evolocumab [Supplementary Concept]),” hepatica”, “AMG-145”, “AMG 145”, “PCSK9 antibody”, “antibody PCSK9”, “PCSK9 inhibitor” and “(Lipoprotein(a)[Mesh])”, “Lipoprotein Lp”, “Lipoprotein”, and “‘Hyperlipoproteinemia type II’[Mesh]”, “‘Familial Hypercholesterolemia’”, “‘Familial Hypercholesterolemias’”, “‘Hypercholesterolemia, Familial’” and “Randomized Controlled Trial (Publication Type),” “Clinical Study”, “Clinical Trial”, “Controlled Clinical Trial”, “Randomized Controlled Trial”, “Equivalence Trial”, “Pragmatic Clinical Trial”, “Randomized”, and “randomly” were used to search for alirocumab/evolocumab and FH. Reference lists of the retrieved studies were manually checked to identify further relevant studies.

**Study selection**

All studies that met the following inclusion criteria were included: (1) randomized, placebo-controlled trial; (2) investigating the impact of alirocumab/evolocumab vs. placebo on plasma/serum concentrations of the Lp(a); (3) providing sufficient information on Lp(a) at baseline and at the end of follow-up in each group or providing the net change values; (4) studies limited to humans and adults (> 18 years), no area, sex limited; (5) longer than 8-week treatment duration. Exclusion criteria were: (1) non-randomized controlled trials; (2) lack of a placebo group; (3) observational studies with case-control, cross-sectional, cohort design, or open-label extension; (4) phase 1 clinical trial; (5) lack of sufficient information on baseline or follow-up lipid profile concentrations; (6) paediatric patients; case reports, letters, reviews, conference proceedings, commentaries, and publications in which the information of Lp(a) that could not be ascertained; (7) duplicate publications or unpublished studies.

**Data extraction**

Two authors (DH and ZY) independently reviewed the titles and abstracts of articles found in the electronic searches for potential eligible studies to review, and independently evaluated the complete with the inclusion criteria and resolved any disagreements with discussion or involvement of a third author (YS). (1) First author’s name; (2) year of publication; (3) study phase; (4) subgroup within study; (5) number of participants; (6) age, gender; (7) baseline of LDL-C, Lp(a), mean of Lp(a) reduction; and (8) treatment duration.

**Quality assessment**

Risk of bias was assessed using the Cochrane risk of bias tool for RCTs [25]. Two researchers assessed quality of eligible studies, and discrepancies were resolved by a third reviewer. The following items were performed: selection bias (randomization and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (differential loss to follow-up), reporting bias (selective reporting), and other sources of bias. “Low risk”, “unclear risk”, and “high risk” were used to evaluate each trial to determine the bias levels.

**Data synthesis and statistical analysis**

Review Manager (RevMan 5.3) and Stata 15.1 software were used to undertake this meta-analysis. For all efficacy outcomes, Lp(a)
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levels were continuous variables and reported as mean difference (MD) and 95% confidence interval (CI). The mean difference and the 95% CI were calculated for continuous outcomes, and p-value < 0.05 was considered significant. If the outcome weren’t reported MD, while reported in median and range (or 95%), mean, which were estimated using the method described by. Wan et al. [26]. Heterogeneity was determined by calculating the I² statistic; p > 0.1 and I² < 50% representing low heterogeneity, p < 0.1 and 50% < I² < 75% representing moderate heterogeneity, and p < 0.1 and I² > 75% representing high heterogeneity. Outcomes were calculated by fixed-effects models under no or low inconsistency (I² < 50%), while moderate and high heterogeneity were pooled based on random-effects models. Funnel plot and Egger’s weighted regression tests were employed to assess the publication bias in the meta-analysis.

Results

Study selection and characteristics

Our search strategy identified and reviewed 956 potential articles. After excluding 223 duplicated studies, the remaining 733 articles were screened for titles and abstracts, and 634 articles were exclude based on our inclusion or exclusion criteria. We further excluded 88 studies, of which 6 were repeat published, 19 were not RCTs, 7 had unusable data, 4 were non-FH, and 52 were conference articles. Finally, 11 studies were included in our meta-analysis. The study selection is shown in Figure 1.

A total of 11 studies, including 13 RCTs, were published between 2012 and 2020 with low risk of bias, of which 5 were phase II studies and 8 were phase III studies (Tab. 1) [27–37]. A total of 2408 participants were included, comprising 1611 participants in the alirocumab/evolocumab group and 797 in the placebo group. The detailed baseline characteristics and the lipid profile of the participants are shown in Table 1.

Risk of bias in the included studies

Risk of bias were assessed using the Cochrane risk of bias tool for RCTs. Two researchers (DH and ZY) assessed the quality of eligible studies, and discrepancies were resolved by a third reviewer (YS). Only one study had high risk of bias for selective reporting, and 2 trials showed high risk of bias regarding blinding of outcome assessment. Also, one study showed unclear risk of bias on allocation concealment and performance bias. All selected studies presented a relatively high evaluated quality and low risk of bias (Supplementary File — Fig. S1).

Efficacy outcomes of alirocumab/evolocumab on percentage of lipoprotein (a) [Lp(a)] concentration reduction

When data were pooled, alirocumab/evolocumab showed a significant efficacy in reducing Lp(a) (weighted mean difference [WMD]: –20.10%, 95% CI: –25.59%...
<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>Type</th>
<th>Treatment duration</th>
<th>Drugs/control</th>
<th>Subgroup within study</th>
<th>Patients (n)</th>
<th>Mean age years ± SD</th>
<th>Male n (%)</th>
<th>Mean LDL-C ± SD [mg/dl]</th>
<th>Mean Lp (a) ± SD [mg/dl]</th>
<th>Mean Lp (a) ± SD reduction [mg/dl]</th>
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<tr>
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<td>II</td>
<td>HeFH</td>
<td>12W</td>
<td>A:150 mg/PBO, Q2W</td>
<td>Experimental</td>
<td>62</td>
<td>53.7 ± 9.7</td>
<td>38 (61.2)</td>
<td>155.7 ± 41.1</td>
<td>40.5 ± 88.2</td>
<td>-5.71 ± 23.41</td>
<td>[27]</td>
</tr>
<tr>
<td>Raal et al. 2012*</td>
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<td>HeFH</td>
<td>12W</td>
<td>E:350,420mg/PBO, Q4W</td>
<td>Experimental</td>
<td>111</td>
<td>49.7 ± 13.3</td>
<td>65 (58.6)</td>
<td>154.4 ± 42.5</td>
<td>38.0 ± 124.4</td>
<td>-8.85 ± 23.37</td>
<td>[28]</td>
</tr>
<tr>
<td>Raal et al. 2015 a*</td>
<td>III</td>
<td>HeFH</td>
<td>12W</td>
<td>E:140 mg/PBO, Q2W</td>
<td>Experimental</td>
<td>110</td>
<td>51.9 ± 12.0</td>
<td>46 (41.8)</td>
<td>154.4 ± 42.5</td>
<td>61.0 ± 131.1</td>
<td>-13.18 ± 22.74</td>
<td>[29]</td>
</tr>
<tr>
<td>Kastelein et al. 2015 a*</td>
<td>II</td>
<td>HeFH</td>
<td>78W</td>
<td>A:75 mg/PBO, Q2W</td>
<td>Experimental</td>
<td>323</td>
<td>52.1 ± 12.9</td>
<td>180 (55.7)</td>
<td>144.8 ± 2.9</td>
<td>51.5 ± 2.8</td>
<td>-12.98 ± 25.12</td>
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<tr>
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<td>HeFH II</td>
<td>78W</td>
<td>A:75 mg /PBO, Q2W</td>
<td>Experimental</td>
<td>167</td>
<td>53.2 ± 12.9</td>
<td>86 (51.5)</td>
<td>134.6 ± 3.2</td>
<td>49.9 ± 5.4</td>
<td>-15.12 ± 23.19</td>
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<tr>
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<td>III</td>
<td>HoFH</td>
<td>12W</td>
<td>E:420 mg /PBO, Q4W</td>
<td>Experimental</td>
<td>33</td>
<td>30.0 ± 12.0</td>
<td>17 (51.5)</td>
<td>355.1 ± 135.1</td>
<td>76.0 ± 88.1</td>
<td>-7.14 ± 23.13</td>
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</tr>
<tr>
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<td>78W</td>
<td>A:150 mg /PBO, Q2W</td>
<td>Experimental</td>
<td>72</td>
<td>49.8 ± 14.2</td>
<td>35 (48.6)</td>
<td>196.3 ± 57.9</td>
<td>22.0 ± 31.1</td>
<td>-5.17 ± 31.17</td>
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<td>HeFH</td>
<td>24W</td>
<td>A:75 mg/PBO, Q2W</td>
<td>Experimental</td>
<td>144</td>
<td>60.3 ± 9.7</td>
<td>84 (58.3)</td>
<td>142.8 ± 27.0</td>
<td>16.8 ± 19.1</td>
<td>-6.64 ± 21.6</td>
<td>[33]</td>
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<td>Moriarty et al. 2016</td>
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<td>HeFH</td>
<td>12W</td>
<td>A:75 mg /PBO, Q2W</td>
<td>Experimental</td>
<td>41</td>
<td>59.5 ± 9.2</td>
<td>26 (63.4)</td>
<td>174.0 ± 51.4</td>
<td>21.0 ± 36.3</td>
<td>-1.05 ± 37.78</td>
<td>[34]</td>
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<tr>
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<td>HoFH</td>
<td>48W</td>
<td>E:420mg/PBO QM</td>
<td>Experimental</td>
<td>289</td>
<td>50.2 ± 12.4</td>
<td>165 (57.1)</td>
<td>154.5 ± 46.3</td>
<td>63.0 ± 128.1</td>
<td>-15.12 ± 27.20</td>
<td>[35]</td>
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<td>Santos et al. 2020*</td>
<td>II</td>
<td>HeFH</td>
<td>24W</td>
<td>E:420mg/PBO QM</td>
<td>Experimental</td>
<td>104</td>
<td>13.7 ± 2.3</td>
<td>61 (58.6)</td>
<td>185.0 ± 45.0</td>
<td>50.5 ± 80.4</td>
<td>-3.74 ± 66.08</td>
<td>[36]</td>
</tr>
<tr>
<td>Blom et al. 2020</td>
<td>III</td>
<td>HoFH</td>
<td>12W</td>
<td>A:150mg/PBO Q2W</td>
<td>Experimental</td>
<td>45</td>
<td>42.3 ± 14.1</td>
<td>21 (46.7)</td>
<td>295.0 ± 154.6</td>
<td>36.0 ± 42.9</td>
<td>-7.06 ± 26.83</td>
<td>[37]</td>
</tr>
</tbody>
</table>

SD — standard deviation; LDL-C — low-density lipoprotein cholesterol; Lp(a) — lipoprotein a; HeFH — homozygous familial hypercholesterolaemia; HoFH — heterozygous familial hypercholesterolaemia; A — alirocumab; E — evolocumab; PBO — placebo; Q2W — every 2 weeks; Q4W — every 4 weeks; QM — every month; *FH I was performed at 89 sites across North America, Europe, and South Africa; FH II was performed across 26 sites in Europe; #The concentration of Lp (a) was expressed as nmol/L
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REVIEW

Fig. 2. Forest plots depicting the effect of alirocumab/evolocumab on percentage of lipoprotein (a) [Lp(a)] concentration reduction. WMD — weighted mean difference; CI — confidence interval

Figure 2. Forest plots depicting the effect of alirocumab/evolocumab on percentage of lipoprotein (a) [Lp(a)] concentration reduction. WMD — weighted mean difference; CI — confidence interval

Efficacy outcomes of alirocumab/evolocumab

All-cause adverse events (AEs) between alirocumab/evolocumab groups and placebo groups were used to evaluate efficacy outcomes. Out of 2408 patients, a total of 1611 in the alirocumab/evolocumab arm, and 797 patients in the placebo group experienced all-cause AEs (relative risk [RR]: 1.06, 95% CI: 1.00–1.12), which means there were no significant differences between the 2 groups (p = 0.109, Supplementary File — Fig. S7).

Meta-regression analysis

To assess the impact of baseline Lp(a) concentrations on the effect of alirocumab/evolocumab on Lp(a) levels, a random-effects meta-regression was undertaken. No significant relationship between baseline age (p = 0.548) and male sex (p = 0.561) was observed. However, the result showed that the more intense the LDL-C level decrease, the greater the Lp(a) level decline (p = 0.016, Supplementary File — Fig. 8).

Discussion

The results of this meta-analysis, based on 13 RCTs involving 2408 participants, significantly suggested that alirocumab/evolocumab could significantly reduce
Lp(a) concentrations in patients with FH, by about 20%, irrespective of the type of PCSK9 inhibitor, patient characteristics, treatment duration, comparison of treatment differences, and baseline Lp(a) concentrations.

It is worth noting that a high degree of heterogeneity of Lp(a) percentage reduction was found in this meta-analysis. Thus, we applied subgroup analyses, and the heterogeneity still existed, and these data were analysed with a random-effect model. Subgroups were analysed for differences in type of drugs (alirocumab or evolocumab), treatment duration (12 weeks or ≥ 24 weeks), characteristics of patients (HoFH or HeFH). Variation in the unique protein structurally of Lp(a) and a strong inverse relationship between the size of the apo(a) subtype and the plasma concentration of Lp(a) in humans made it a challenge to develop an accurate immunoassay for Lp(a) [38]. Although in our meta-analysis no difference reported in the 2 types of drugs, other studies have not provided accurate results, and more evidence is needed. There was no or low heterogeneity in the meta-analysis of Lp(a) absolute reduction.

As far as we know, this is the first meta-analysis of all published RCTs data to compare the association between alirocumab/evolocumab and Lp(a) levels in FH adult patients, with percentage concentration reduction. Although previously pooled analyses have been evaluated, they might have been limited by a single type of monoclonal antibody or healthy volunteers among the participants, or phase I clinical trials [39–41]. Interestingly, we obtained a similar result, with PCSK9 inhibitors causing a significant and sustained decrease of Lp(a) levels, from 15.66% to 25.21% [39], and a single-lipid-unit real-life setting after 6 months of PCSK9 therapy showed significant Lp(a) concentration reduction of 12.3 mmol/L [42], and a new study of alirocumab in patients with HeFH showed a reduction of Lp(a) levels of 7.88 mg/dL [43]. Waldmann et al. [44] suggested that evolocumab reduced Lp(a) levels 9.0 mg/dL in the type III hyperlipidaemia. Several studies observed that alirocumab/evolocumab could significantly reduce Lp(a) from baseline in non-FH [44–46]. In a real-world clinical setting, anti-PCSK9 drugs have been shown to be effective, safe, and well-tolerated, with effects comparable to those reported in large RCTs [46].

Increasing evidence, including epidemiological, genome-wide association, and Mendelian randomization, suggests that elevated Lp(a) is a common, independent, and causal risk factor for ASCVD [7, 47], which led to a recent consensus statement from HEART UK, which provided recommendations for measurement in clinical practice and reviews of therapeutic strategies for reducing the risk of ASCVD in individuals with high Lp(a) levels [48]. Although the mechanism of Lp(a) promoting atherosclerosis remains uncertain, it is generally accepted that due to its low-density lipoprotein (LDL) moiety, the homology with plasminogen promotes thrombosis, the oxidized phospholipids which mediate arterial wall inflammation promoted vascular inflammation [49]. Like LDL-C, Lp(a) could also be oxidized and engulfed by macrophages through scavenger receptors after entering the intima of blood vessels, and promote the formation of foam cells and thrombosis [50].

Our meta-analysis confirmed that alirocumab/evolocumab could significantly reduce Lp(a) concentrations of FH, although the mechanisms are still inadequately understood. Current hypotheses include several assumptions: (1) via the LDLR increased clearance of Lp(a) particles [51]; (2) via additional receptors increased clearance of Lp(a) [52]; and (3) reduction in apo(a) production, secretion, and/or assembly [53, 54]. Watts et al. [55] found that alirocumab reduces elevated Lp(a) concentrations in plasma by accelerating Lp(a) particle catabolism, possibly due to significantly upregulated and/or reduced competition for these receptors by Lp(a) and LDL particles. Reyes-Soffer et al. [56] found that evolocumab treatment of homozygous FH (HoFH) was associated with reductions in Lp(a) levels, although this was suggestive and not conclusive. If LDLR was the major pathway for Lp(a) clearance, then PCSK9 inhibitor antagonism should produce a reduced ratio of LDL-C to Lp(a), with patients achieving the 2:1 ratio seen in large clinical trials (LDL-C 50–60%: Lp(a) 25–30%) [57]. Nevertheless, 2 recent studies have emphasized the fact that a significant proportion of patients showed LDL-C reduction with little or no reduction in Lp(a), and defined the ratio of LDL-C:Lp(a) reduction as 3.5:1, which corroborates a ≥ 35% reduction in LDL-C and a ≤ 10% reduction in Lp(a) [58, 59]. Unlike LDL, LDLR is not the primary scavenging receptor for Lp(a), while the exact role of LDLR in Lp(a) catabolism remains controversial. Cain et al. [60] reported that LDLR has no effect on Lp(a) because there is evidence that Lp(a) catabolism in LDLR-/- mice was similar to that in wild-type mice. In addition, plasma Lp(a) levels are largely insensitive to statins [61]; these drugs work by increasing the abundance of LDLR in the liver, which again suggests that LDLR plays no role in Lp(a) catabolism [62]. Evidence to support the role of LDLR has also been reported. Hofmann et al. [63] found that Lp(a) clearance was significantly increased in LDLR overexpressing mice. Results of a cross-sectional analysis of 1960 FH patients, compared to control subjects, showed significantly higher Lp(a) concentrations in patients with null LDLR alleles [64]. The exact mechanism of Lp(a) reduction by PCSK9 inhibitors is still unclear and merits further study.
In this study, no obvious difference in AEs was found between the 2 groups. Although Lp(a) is an independent risk factor for ASCVD, it is difficult to attribute the clinical benefit and AEs to Lp(a) reduction, and currently no drugs can selectively reduce Lp(a), including statins [65]. Approximately 30–50% of HeFH patients have elevated Lp(a) levels, and the cumulative burden of high Lp(a) is a strong driver of ASCVD for them [9]. In a multi-centre cohort study conducted in the Netherlands, which included 2400 patients with heterozygous FH, the RR of ASCVD for Lp(a) concentrations > 30 mg/dL were 1.46 (95% CI: 1.20 to 1.79, p < 0.0001) [66]. Liu et al. [67] found that, based on a long-term cohort study of 6175 patients, the prevalence of severe AEs was found to be significantly higher among patients with high Lp(a) levels. Based on our data, alirocumab/evolocumab currently serves as a satisfactory treatment.

The neurocognitive safety of FH lipid-lowering therapy is another important issue. Currently, no definitive evidence exists for the association between statin therapy and neurocognitive AEs [68]. Harvey et al. [69] reported no association between neurocognitive AEs and alirocumab treatment, which involved 14 RCTs. Janik et al. [70] reported on the approved dose regimen of alirocumab treatment for patients with HeFH or non-FH, with no significant effect on neurocognitive function over 96 weeks of treatment. Raal et al. [31] found that no neurocognitive AEs were reported in HeFH treated with evolocumab.

This meta-analysis has some limitations. Firstly, although high heterogeneity was evident across several comparisons, there was no publication bias, and the results were consistent across subgroups. Secondly, only 2 PCSK9 inhibitors, alirocumab and evolocumab, were included, and others, like icilisiran, LY3015014, and RG7652, were excluded. Thirdly, research on paediatric and adolescent patients was not included. Recently studies have shown that the 2 PCSK9 inhibitors had a good therapeutic effect on these patients [71, 72]. Finally, like other meta-analyses, our study was a retrospective analysis, and more evidence from large, randomized trials is needed to confirm these findings.

Conclusion

Anti-PCSK9 drugs (alirocumab and evolocumab) may be effective therapy for reducing serum Lp(a) levels in FH, and no differences were observed in treatment durations, participant characteristics, and other aspects of the 2 types of PCSK9 inhibitors. However, further experimental studies and RCTs are warranted to clarify the mechanism of PCSK9 inhibitors in lowering Lp(a) concentrations in FH.

Data availability statement

The aggregated data presented in the study are included in the article/supplementary material, and further data access inquiries can be directed to the corresponding authors.

Author contributions

D.H., Z.Y., C.Z., and Z.F. designed the study, interpreted the data, and drafted and revised the article. Y.R., L.J., and H.Z. collected and analysed the data. Z.L. and Y.S. performed the systematic literature search and contributed the writing of the article. All authors have read and agreed to the published version of the manuscript.

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References

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