Submitted: 07.10.2022
Accepted: 02.04.2023
Early publication date: 12.06.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0036
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 3/2023

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

Haibing Dai[1, 2]*, Yonglin Zhu[1, 2]*, Zuyi Chen[1, 2]*, Renqing Yan[1, 2], Jinsong Liu[1, 2], Ziyun He[1, 2], Lin Zhang[3], Feng Zhang[1, 2], Shengkai Yan[1]

[1]Department of Laboratory Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China
[2]College of Laboratory Medicine, Zunyi Medical University, Zunyi, China
[3]School 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 PSCK9 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

Shengkai Yan, Department of Laboratory Medicine, Affiliated Hospital of Zunyi Medical University, Zunyi, China; e-mail: yanshengkai@sina.com

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 invertase 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])", "repatha", "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", "Hypercholesterolemias, 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)

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 I^2 statistic; $p > 0.1$ and $I^2 < 50\%$ representing low heterogeneity, $p < 0.1$ and $50\% < I^2 < 75\%$ representing moderate heterogeneity, and $p < 0.1$ and $I^2 > 75\%$ representing high heterogeneity. Outcomes were calculated by fixed-effects models under no or low inconsistency ($I^2 < 50\%$), 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%

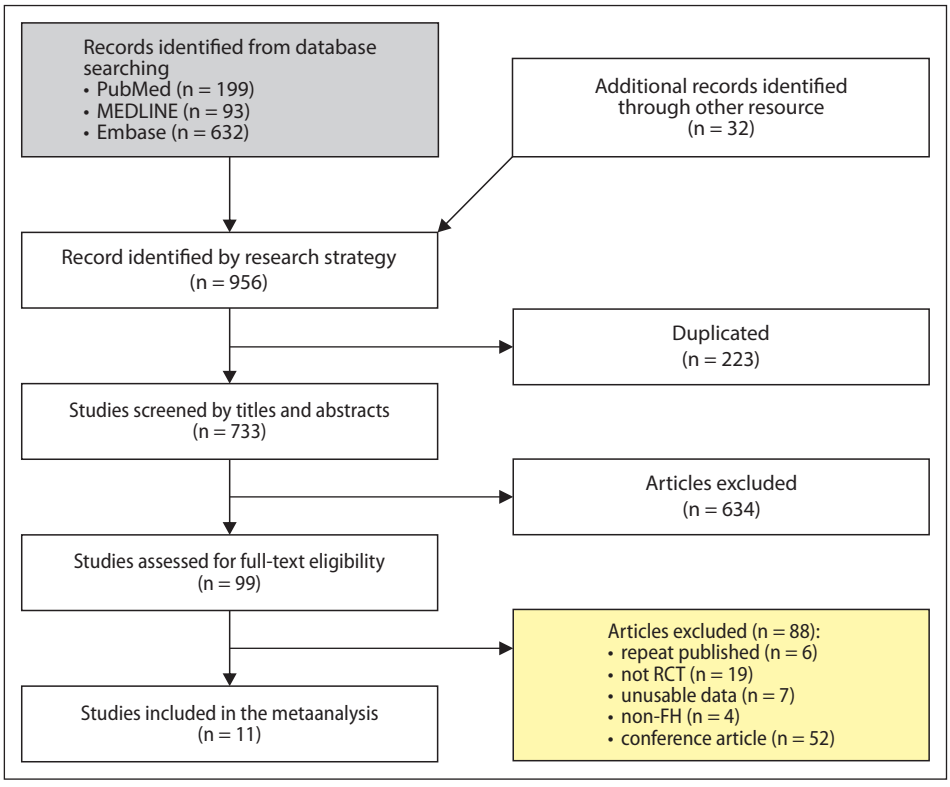

Figure 1. *PRISMA flow diagram of selection of studies included in the meta-analysis. RCT — randomized controlled trial; non-FH — non-familial hypercholesterolaemia*

Table 1. *The baseline characteristics and lipid profile of subjects*

Author	Phase	Type	Treatment duration	Drugs/control	Subgroup within study	Patients (n)	Mean age years ± SD	Male n (%)	Mean LDL-C ± SD [mg/dl]	Mean Lp (a) ± SD [mg/dl]	Mean Lp (a) ± SD reduction [mg/dl]	Reference
Stein et al. 2012	II	HeFH	12W	A:150 mg/PBO, Q2W	Experimental	62	53.7 ± 9.7	38 (61.2)	155.7 ± 41.1	40.5 ± 88.2	–5.71 ± 23.41	[27]
					Placebo	15	51.9 ± 9.6	9 (60.0)	150.1 ± 33.9	31.0 ± 91.2	–1.21 ± 13.61	
Raal et al. 2012#	II	HeFH	12W	E:350,420mg/PBO, Q4W	Experimental	111	49.7 ± 13.3	65 (58.6)	154.4 ± 42.5	38.0 ± 124.4	–8.85 ± 23.37	[28]
					Placebo	56	49.3 ± 11.3	24 (42.9)	162.1 ± 42.5	45.0 ± 105.4	–1.84 ± 23.19	
Raal et al. 2015 a#	III	HeFH	12W	E:140 mg/PBO, Q2W	Experimental	110	52.6 ± 12.3	66 (60.0)	162.1 ± 50.2	77.5 ± 130.7	–17.75 ± 24.61	[29]
					Placebo	54	51.1 ± 14.2	29 (53.7)	150.5 ± 34.7	44.0 ± 60.0	–3.83 ± 24.14	
Raal et al. 2015 b#	III	HeFH	12W	E: 420 mg/PBO, QM	Experimental	110	51.9 ± 12.0	46 (41.8)	154.4 ± 42.5	61.0 ± 131.1	–13.18 ± 22.74	[29]
					Placebo	55	46.8 ± 12.1	24 (43.6)	154.4 ± 42.5	87.0 ± 135.6	5.83 ± 23.46	
Kastelein et al. 2015 a*	II	HeFH	78W	A:75 mg/PBO, Q2W	Experimental	323	52.1 ± 12.9	180 (55.7)	144.8 ± 2.9	51.5 ± 2.8	–12.98 ± 25.12	[30]
					Placebo	163	51.7 ± 12.3	94 (57.7)	144.4 ± 3.7	46.9 ± 4.0	–3.52 ± 25.53	
Kastelein et al. 2015 b*	II	HeFH II	78W	A:75 mg /PBO, Q2W	Experimental	167	53.2 ± 12.9	86 (51.5)	134.6 ± 3.2	49.9 ± 5.4	–15.12 ± 23.19	[30]
					Placebo	82	53.2 ± 12.5	45 (54.9)	134.0 ± 4.6	50.9 ± 6.6	–5.09 ± 22.50	
Raal et al. 2015#	III	HoFH	12W	E:420 mg /PBO, Q4W	Experimental	33	30.0 ± 12.0	17 (51.5)	355.1 ± 135.1	76.0 ± 88.1	–7.14 ± 23.13	[31]
					Placebo	16	32.0 ± 14.0	8 (50.0)	355.8 ± 142.8	128.0 ± 89.6	3.08 ± 20.74	
Ginsberg et al. 2016	III	HeFH	78W	A:150 mg /PBO, Q2W	Experimental	72	49.8 ± 14.2	35 (48.6)	196.3 ± 57.9	22.0 ± 31.1	–5.17 ± 31.18	[32]
					Placebo	35	52.1 ± 11.2	22 (62.9)	201.0 ± 43.4	30.0 ± 23.0	–2.61 ± 29.58	
Teramoto et al. 2016	III	HeFH	24W	A:75 mg/PBO, Q2W	Experimental	144	60.3 ± 9.7	84 (58.3)	142.8 ± 27.0	16.8 ± 19.1	–6.64 ± 21.60	[33]
					Placebo	72	61.8 ± 9.0	47 (65.3)	142.8 ± 27.1	14.7 ± 25.2	0.37 ± 21.21	
Moriarty et al. 2016	III	HeFH	12W	A:75 mg /PBO, Q2W	Experimental	41	59.5 ± 9.2	26 (63.4)	174.0 ± 51.4	21.0 ± 36.3	–1.05 ± 37.78	[34]
					Placebo	21	57.0 ± 10.5	10 (47.6)	195.0 ± 66.9	18.0 ± 42.2	–0.16 ± 36.66	
Hovingh et al. 2017#	III	HeFH	48W	E:420mg/PBO QM	Experimental	289	50.2 ± 12.4	165 (57.1)	154.5 ± 46.3	63.0 ± 128.1	–15.12 ± 27.20	[35]
					Placebo	151	52.0 ± 12.2	88 (58.3)	150.5 ± 38.6	44.0 ± 131.1	0.0 ± 25.80	
Santos et al. 2020#	II	HeFH	24W	E:420mg/PBO QM	Experimental	104	13.7 ± 2.3	61 (58.6)	185.0 ± 45.0	50.5 ± 80.4	–3.74 ± 66.08	[36]
					Placebo	53	13.7 ± 2.5	27 (50.9)	183.0 ± 47.2	34.0 ± 93.3	0.58 ± 69.64	
Blom et al. 2020	III	HoFH	12W	A:150mg/PBO Q2W	Experimental	45	42.3 ± 14.1	21 (46.7)	295.0 ± 154.6	36.0 ± 42.9	–7.06 ± 26.83	[37]
					Placebo	24	45.4 ± 15.8	13 (54.2)	259.6 ± 35.9	32.5 ± 30.0	2.86 ± 26.45	

SD — standard deviation; LDL-C — low-density lipoprotein cholesterol; Lp(a) — lipoprotein a; HeFH — homozygotous familial hypercholesterolaemia; HoFH — heterozygotous 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

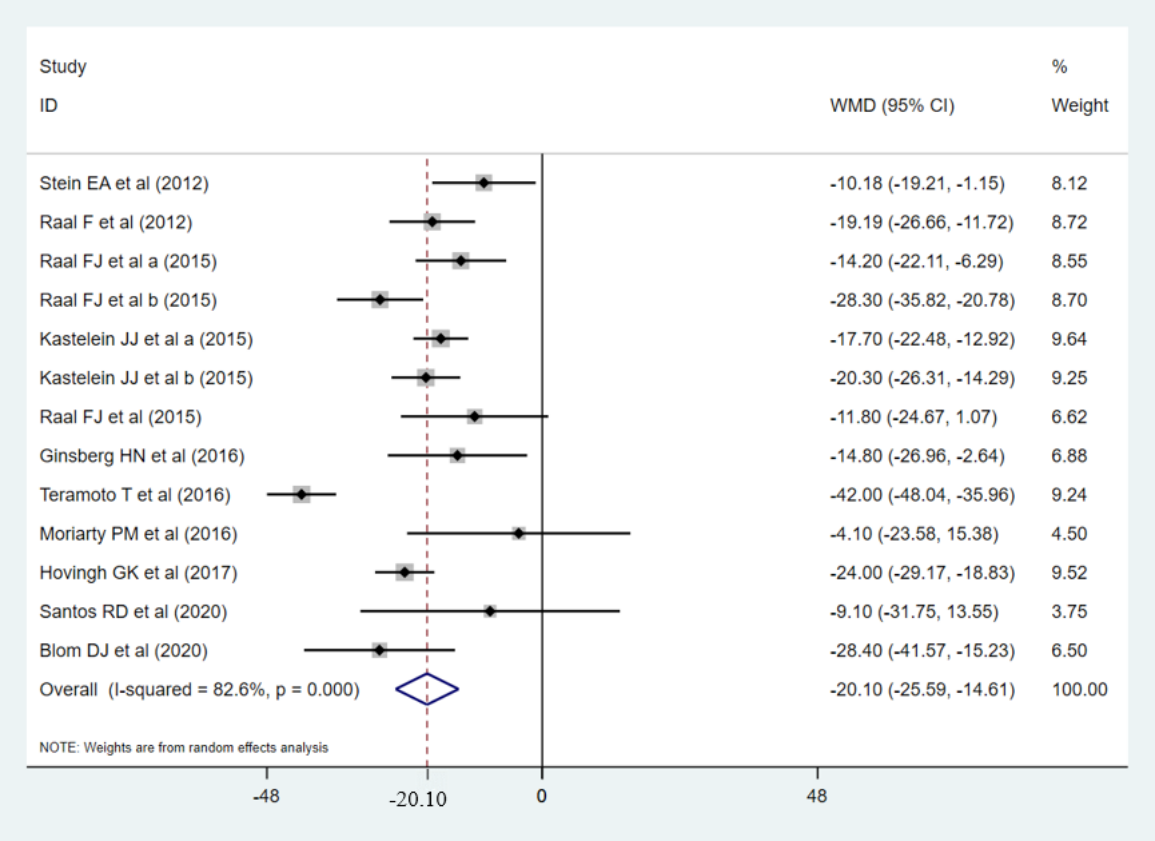

Figure 2. *Forest plots depicting the effect of alirocumab/evolocumab on percentage of lipoprotein (a) [Lp(a)] concentration reduction. WMD — weighted mean difference; CI — confidence interval*

to –14.61%; Fig. 2) compared with placebo. There was a high heterogeneity between each study (I^2 = 82.6%, p < 0.001), so we chose the random-effect model.

To assess the potential discrepancies, we applied the subgroup analyses based on the characteristics of trials and participants (Supplementary File — Fig. S2–4). 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%). When studies were classified by treatment duration, the efficacy of 12-week duration group (WMD: –17.61%, 95% CI: –23.84% to –11.38%) was lower than the ≥ 24-week duration group (WMD: –22.81%, 95% CI: –31.56% to –14.07%). The analysis stratified by participants' characteristics also supported the result that no differential effect of alirocumab/evolocumab therapy on plasma Lp(a) concentrations was observed (HeFH WMD: –20.07%, 95% CI: –26.07% to –14.08%; HoFH WMD: –20.04%, 95% CI: –36.31% to –3.77%). Sensitivity analysis for all studies was performed by leave-one-out. Nevertheless, the result showed no significant change (Supplementary File — Fig. 5). Neither funnel plots (Supplementary File — Fig. 6) nor Egger's regression test (p = 0.274) showed publication bias.

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 structure 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 1 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 nmol/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 inclisiran, 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 PSCK9 inhibitors in lowing 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.

Funding

This work was partially sponsored by grants from the National Natural Science Foundation of China (No. 82070916) and Zunyi Science and Technology Planning Project (Zun Shi Ke He HZ [2021] No. 185).

References

1. Jackson CL, Zordok M, Kullo IJ. Familial hypercholesterolemia in Southeast and East Asia. Am J Prev Cardiol. 2021; 6: 100157, doi: 10.1016/j.ajpc.2021.100157, indexed in Pubmed: 34327494.
2. Amerizadeh A, Javanmard SH, Sarrafzadegan N, et al. Familial Hypercholesterolemia (FH) Registry Worldwide: A Systematic Review. Curr Probl Cardiol. 2022; 47(10): 100999, doi: 10.1016/j.cpcardiol.2021.100999, indexed in Pubmed: 34571102.
3. Gidding SS, Champagne MA, de Ferranti SD, et al. American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015; 132(22): 2167–2192, doi: 10.1161/CIR.0000000000000297, indexed in Pubmed: 26510694.
4. Faggiano P, Pirillo A, Griffo R, et al. Centro Studi e Formazione - Italian Association for Cardiovascular Prevention and Rehabilitation. Prevalence and management of familial hypercholesterolemia in patients with coronary artery disease: The heredity survey. Int J Cardiol. 2018; 252: 193–198, doi: 10.1016/j.ijcard.2017.10.105, indexed in Pubmed: 29249427.
5. Anastasiou G, Sakka E, Blathra E, et al. Lipoprotein(a): A Concealed Precursor of Increased Cardiovascular Risk? A Real-World Regional Lipid Clinic Experience. Arch Med Res. 2021; 52(4): 397–404, doi: 10.1016/j.arcmed.2020.12.003, indexed in Pubmed: 33380360.
6. Cao YX, Liu HH, Li S, et al. A Meta-Analysis of the Effect of PCSK9-Monoclonal Antibodies on Circulating Lipoprotein (a) Levels. Am J Cardiovasc Drugs. 2019; 19(1): 87–97, doi: 10.1007/s40256-018-0303-2, indexed in Pubmed: 30229525.
7. Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019; 290: 140–205, doi: 10.1016/j.atherosclerosis.2019.08.014, indexed in Pubmed: 31591002.
8. Vuorio A, Watts GF, Schneider WJ, et al. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. J Intern Med. 2020; 287(1): 2–18, doi: 10.1111/joim.12981, indexed in Pubmed: 31858669.
9. Pavanello C, Pirazzi C, Bjorkman K, et al. Individuals with familial hypercholesterolemia and cardiovascular events have higher circulating Lp(a) levels. J Clin Lipidol. 2019; 13(5): 778–787.e6, doi: 10.1016/j.jacl.2019.06.011, indexed in Pubmed: 31371270.
10. Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. Nat Rev Cardiol. 2019; 16(1): 9–20, doi: 10.1038/s41569-018-0052-6, indexed in Pubmed: 29973710.
11. Burgess S, Ference BA, Staley JR, et al. European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Men-

delian Randomization Analysis. JAMA Cardiol. 2018; 3(7): 619–627, doi: 10.1001/jamacardio.2018.1470, indexed in Pubmed: 29926099.
12. Wilson PWF, Polonsky TS, Miedema MD, et al. Systematic Review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139(25): e1144–e1161, doi: 10.1161/CIR.0000000000000626, indexed in Pubmed: 30586775.
13. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Peripheral Vascular Disease. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022; 42(1): e48–e60, doi: 10.1161/ATV.0000000000000147, indexed in Pubmed: 34647487.
14. Madsen CM, Kamstrup PR, Langsted A, et al. Lipoprotein(a)-Lowering by 50 mg/dL (105 nmol/L) May Be Needed to Reduce Cardiovascular Disease 20% in Secondary Prevention: A Population-Based Study. Arterioscler Thromb Vasc Biol. 2020; 40(1): 255–266, doi: 10.1161/ATVBAHA.119.312951, indexed in Pubmed: 31578080.
15. Nordestgaard BG, Chapman MJ, Ray K, et al. European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010; 31(23): 2844–2853, doi: 10.1093/eurheartj/ehq386, indexed in Pubmed: 20965889.
16. Wu MF, Xu KZ, Guo YG, et al. Lipoprotein(a) and Atherosclerotic Cardiovascular Disease: Current Understanding and Future Perspectives. Cardiovasc Drugs Ther. 2019; 33(6): 739–748, doi: 10.1007/s10557-019-06906-9, indexed in Pubmed: 31655942.
17. Page MM, Ekinci EI, Burnett JR, et al. Lipoprotein apheresis and PCSK9 inhibitors for severe familial hypercholesterolaemia: Experience from Australia and New Zealand. J Clin Apher. 2021; 36(1): 48–58, doi: 10.1002/jca.21839, indexed in Pubmed: 32911577.
18. Li S, Zhang Y, Xu RX, et al. Proprotein convertase subtilisin-kexin type 9 as a biomarker for the severity of coronary artery disease. Ann Med. 2015; 47(5): 386–393, doi: 10.3109/07853890.2015.1042908, indexed in Pubmed: 26153823.
19. Ceballos-Macías JJ, Lara-Sánchez C, Flores-Real J, et al. PCSK-9 Inhibitors in a Real-World Setting and a Comparison Between Alirocumab and Evolocumab in Heterozygous FH Patients. J Endocr Soc. 2021; 5(1): bvaa180, doi: 10.1210/jendso/bvaa180, indexed in Pubmed: 33367195.
20. Torres E, Goicoechea M, Hernández A, et al. Efficacy of Evolocumab *vs* low-density lipoprotein cholesterol apheresis in patients with familial hypercholesterolemia and high cardiovascular risk (EVOLAFER01). J Clin Apher. 2020; 35(1): 9–17, doi: 10.1002/jca.21752, indexed in Pubmed: 31663632.
21. Mahmood T, Minnier J, Ito MK, et al. Discordant responses of plasma low-density lipoprotein cholesterol and lipoprotein(a) to alirocumab: A pooled analysis from 10 ODYSSEY Phase 3 studies. Eur J Prev Cardiol. 2021; 28(8): 816–822, doi: 10.1177/2047487320915803, indexed in Pubmed: 34298554.
22. Szarek M, Bittner VA, Aylward P, et al. ODYSSEY OUTCOMES Investigators. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. Eur Heart J. 2020; 41(44): 4245–4255, doi: 10.1093/eurheartj/ehaa649, indexed in Pubmed: 33051646.
23. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol. 2014; 176(1): 55–61, doi: 10.1016/j.ijcard.2014.06.049, indexed in Pubmed: 25037695.
24. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535, doi: 10.1136/bmj.b2535, indexed in Pubmed: 19622551.
25. Higgins JPT, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928, doi: 10.1136/bmj.d5928, indexed in Pubmed: 22008217.
26. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14: 135, doi: 10.1186/1471-2288-14-135, indexed in Pubmed: 25524443.
27. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012; 380(9836): 29–36, doi: 10.1016/S0140-6736(12)60771-5, indexed in Pubmed: 22633824.
28. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. Circulation. 2012; 126(20): 2408–2417, doi: 10.1161/CIRCULATIONAHA.112.144055, indexed in Pubmed: 23129602.
29. Raal FJ, Stein EA, Dufour R, et al. RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 331–340, doi: 10.1016/S0140-6736(14)61399-4, indexed in Pubmed: 25282519.
30. Kastelein JJP, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J. 2015; 36(43): 2996–3003, doi: 10.1093/eurheartj/ehv370, indexed in Pubmed: 26330422.
31. Raal FJ, Honarpour N, Blom DJ, et al. TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965): 341–350, doi: 10.1016/S0140-6736(14)61374-X, indexed in Pubmed: 25282520.
32. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. Cardiovasc Drugs Ther. 2016; 30(5): 473–483, doi: 10.1007/s10557-016-6685-y, indexed in Pubmed: 27618825.
33. Teramoto T, Kobayashi M, Tasaki H, et al. Efficacy and Safety of Alirocumab in Japanese Patients With Heterozygous Familial Hypercholesterolemia or at High Cardiovascular Risk With Hypercholesterolemia Not Adequately Controlled With Statins — ODYSSEY JAPAN Randomized Controlled Trial. Circ J. 2016; 80(9): 1980–1987, doi: 10.1253/circj.CJ-16-0387, indexed in Pubmed: 27452202.
34. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016; 37(48): 3588–3595, doi: 10.1093/eurheartj/ehw388, indexed in Pubmed: 27572070.
35. Hovingh GK, Raal FJ, Dent R, et al. Long-term safety, tolerability, and efficacy of evolocumab in patients with heterozygous familial hypercholesterolemia. J Clin Lipidol. 2017; 11(6): 1448–1457, doi: 10.1016/j.jacl.2017.09.003, indexed in Pubmed: 29066265.
36. Santos RD, Ruzza A, Hovingh GK, et al. HAUSER-RCT Investigators. Evolocumab in Pediatric Heterozygous Familial Hypercholesterolemia. N Engl J Med. 2020; 383(14): 1317–1327, doi: 10.1056/NEJMoa2019910, indexed in Pubmed: 32865373.
37. Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and Safety of Alirocumab in Adults With Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol. 2020; 76(2): 131–142, doi: 10.1016/j.jacc.2020.05.027, indexed in Pubmed: 32646561.
38. Lambert G, Thedrez A, Croyal M, et al. The complexity of lipoprotein (a) lowering by PCSK9 monoclonal antibodies. Clin Sci (Lond). 2017; 131(4): 261–268, doi: 10.1042/CS20160403, indexed in Pubmed: 28108631.
39. Li B, Hao PP, Zhang Y, et al. Efficacy and safety of proprotein convertase subtilisin/kexin type 9 monoclonal antibody in adults with familial hypercholesterolemia. Oncotarget. 2017; 8(18): 30455–30463, doi: 10.18632/oncotarget.10762, indexed in Pubmed: 27458166.
40. Djebli N, Martinez JM, Lohan L, et al. Target-Mediated Drug Disposition Population Pharmacokinetics Model of Alirocumab in Healthy Volunteers and Patients: Pooled Analysis of Randomized Phase I/II/III Studies. Clin Pharmacokinet. 2017; 56(10): 1155–1171, doi: 10.1007/s40262-016-0505-1, indexed in Pubmed: 28063030.
41. Eslami SM, Nikfar S, Ghasemi M, et al. Does Evolocumab, as a PCSK9 Inhibitor, Ameliorate the Lipid Profile in Familial Hypercholesterolemia Patients? A Meta-Analysis of Randomized Controlled Trials. J Pharm Pharm Sci. 2017; 20: 81–96, doi: 10.18433/J36C8N, indexed in Pubmed: 28459663.
42. Scicali R, Di Pino A, Ferrara V, et al. Effect of PCSK9 inhibitors on pulse wave velocity and monocyte-to-HDL-cholesterol ratio in familial hypercholesterolemia subjects: results from a single-lipid-unit real-life setting. Acta Diabetol. 2021; 58(7): 949–957, doi: 10.1007/s00592-021-01703-z, indexed in Pubmed: 33745063.
43. Ginsberg HN, Tuomilehto J, Hovingh GK, et al. Impact of Age on the Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia. Cardiovasc Drugs Ther. 2019; 33(1): 69–76, doi: 10.1007/s10557-019-06852-6, indexed in Pubmed: 30734207.
44. Waldmann E, Wu L, Busygina K, et al. Effect of PCSK9 inhibition with evolocumab on lipoprotein subfractions in familial dysbetalipoproteinemia (type III hyperlipidemia). PLoS One. 2022; 17(3): e0265838, doi: 10.1371/journal.pone.0265838, indexed in Pubmed: 35320320.
45. Krempf M, Hopkins PN, Bruckert E, et al. Efficacy and Safety of Alirocumab in Patients With Autosomal Dominant Hypercholesterolemia Associated With Proprotein Convertase Subtilisin/Kexin Type 9 Gain-of-Function or Apolipoprotein B Loss-of-Function Mutations. Am J Cardiol. 2020; 125(6): 880–886, doi: 10.1016/j.amjcard.2019.12.028, indexed in Pubmed: 31932084.

46. Altschmiedová T, Todorovová W, Šnejdrlová N. PCSK9 Inhibitors in Real-world Practice: Analysis of Data from 314 Patients and 2 Years of Experience in a Center of Preventive Cardiology. Curr Atheroscler Rep. 2022; 24(5): 357–363, doi: 10.1007/s11883-022-01008-8, indexed in Pubmed: 35332442.
47. Boffa MB, Koschinsky ML. Proprotein convertase subtilisin/kexin type 9 inhibitors and lipoprotein(a)-mediated risk of atherosclerotic cardiovascular disease: more than meets the eye? Curr Opin Lipidol. 2019; 30(6): 428–437, doi: 10.1097/MOL.0000000000000641, indexed in Pubmed: 31577611.
48. Cegla J, Neely RD, France M, et al. HEART UK Medical, Scientific and Research Committee. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019; 291: 62–70, doi: 10.1016/j.atherosclerosis.2019.10.011, indexed in Pubmed: 31704552.
49. Bergmark C, Dewan A, Orsoni A, et al. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma. J Lipid Res. 2008; 49(10): 2230–2239, doi: 10.1194/jlr.M800174-JLR200, indexed in Pubmed: 18594118.
50. Saeed A, Kinoush S, Virani SS. Lipoprotein (a): Recent Updates on a Unique Lipoprotein. Curr Atheroscler Rep. 2021; 23(8): 41, doi: 10.1007/s11883-021-00940-5, indexed in Pubmed: 34146181.
51. Hoover-Plow J, Huang M. Lipoprotein(a) metabolism: potential sites for therapeutic targets. Metabolism. 2013; 62(4): 479–491, doi: 10.1016/j.metabol.2012.07.024, indexed in Pubmed: 23040268.
52. Watts GF, Chan DC, Somaratne R, et al. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. Eur Heart J. 2018; 39(27): 2577–2585, doi: 10.1093/eurheartj/ehy122, indexed in Pubmed: 29566128.
53. Villard EF, Thedrez A, Blankenstein J, et al. PCSK9 Modulates the Secretion But Not the Cellular Uptake of Lipoprotein(a) Ex Vivo: An Effect Blunted by Alirocumab. JACC Basic Transl Sci. 2016; 1(6): 419–427, doi: 10.1016/j.jacbts.2016.06.006, indexed in Pubmed: 29308438.
54. Kostner KM, Kostner GM. Lipoprotein (a): a historical appraisal. J Lipid Res. 2017; 58(1): 1–14, doi: 10.1194/jlr.R071571, indexed in Pubmed: 27821413.
55. Watts GF, Chan DC, Pang J, et al. PCSK9 Inhibition with alirocumab increases the catabolism of lipoprotein(a) particles in statin-treated patients with elevated lipoprotein(a). Metabolism. 2020; 107: 154221, doi: 10.1016/j.metabol.2020.154221, indexed in Pubmed: 32240727.
56. Reyes-Soffer G, Pavlyha M, Ngai C, et al. Effects of PCSK9 Inhibition With Alirocumab on Lipoprotein Metabolism in Healthy Humans. Circulation. 2017; 135(4): 352–362, doi: 10.1161/CIRCULATIONAHA.116.025253, indexed in Pubmed: 27986651.
57. Korneva VA, Kuznetsova TY, Julius U. Modern Approaches to Lower Lipoprotein(a) Concentrations and Consequences for Cardiovascular Diseases. Biomedicines. 2021; 9(9), doi: 10.3390/biomedicines9091271, indexed in Pubmed: 34572458.
58. Shapiro MD, Minnier J, Tavori H, et al. Relationship Between Low-Density Lipoprotein Cholesterol and Lipoprotein(a) Lowering in Response to PCSK9 Inhibition With Evolocumab. J Am Heart Assoc. 2019; 8(4): e010932, doi: 10.1161/JAHA.118.010932, indexed in Pubmed: 30755061.
59. Raal FJ, Giugliano RP, Sabatine MS, et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. J Lipid Res. 2016; 57(6): 1086–1096, doi: 10.1194/jlr.P065334, indexed in Pubmed: 27102113.
60. Cain WJ, Millar JS, Himebauch AS, et al. Lipoprotein [a] is cleared from the plasma primarily by the liver in a process mediated by apolipoprotein [a]. J Lipid Res. 2005; 46(12): 2681–2691, doi: 10.1194/jlr.M500249-JLR200, indexed in Pubmed: 16150825.
61. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation. 2014; 129(6): 635–642, doi: 10.1161/CIRCULATIONAHA.113.004406, indexed in Pubmed: 24243886.
62. Romagnuolo R, Scipione CA, Marcovina SM, et al. Roles of the low density lipoprotein receptor and related receptors in inhibition of lipoprotein(a) internalization by proprotein convertase subtilisin/kexin type 9. PLoS One. 2017; 12(7): e0180869, doi: 10.1371/journal.pone.0180869, indexed in Pubmed: 28750079.
63. Hofmann SL, Eaton DL, Brown MS, et al. Overexpression of human low density lipoprotein receptors leads to accelerated catabolism of Lp(a) lipoprotein in transgenic mice. J Clin Invest. 1990; 85(5): 1542–1547, doi: 10.1172/JCI114602, indexed in Pubmed: 2139667.
64. Alonso R, Andres E, Mata N, et al. SAFEHEART Investigators. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol. 2014; 63(19): 1982–1989, doi: 10.1016/j.jacc.2014.01.063, indexed in Pubmed: 24632281.
65. Liu T, Yoon WS, Lee SR. Recent Updates of Lipoprotein(a) and Cardiovascular Disease. Chonnam Med J. 2021; 57(1): 36–43, doi: 10.4068/cmj.2021.57.1.36, indexed in Pubmed: 33537217.
66. Jansen ACM, van Aalst-Cohen ES, Tanck MW, et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med. 2004; 256(6): 482–490, doi: 10.1111/j.1365-2796.2004.01405.x, indexed in Pubmed: 15554949.
67. Liu HH, Cao YX, Jin JL, et al. Predicting Cardiovascular Outcomes by Baseline Lipoprotein(a) Concentrations: A Large Cohort and Long-Term Follow-up Study on Real-World Patients Receiving Percutaneous Coronary Intervention. J Am Heart Assoc. 2020; 9(3): e014581, doi: 10.1161/JAHA.119.014581, indexed in Pubmed: 32013705.
68. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med. 2013; 159(10): 688–697, doi: 10.7326/0003-4819-159-10-201311190-00007, indexed in Pubmed: 24247674.
69. Harvey PD, Sabbagh MN, Harrison JE, et al. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: a meta-analysis of individual patient data. Eur Heart J. 2018; 39(5): 374–381, doi: 10.1093/eurheartj/ehx661, indexed in Pubmed: 29186504.
70. Janik MJ, Urbach DV, van Nieuwenhuizen E, et al. Alirocumab treatment and neurocognitive function according to the CANTAB scale in patients at increased cardiovascular risk: A prospective, randomized, placebo-controlled study. Atherosclerosis. 2021; 331: 20–27, doi: 10.1016/j.atherosclerosis.2021.06.913, indexed in Pubmed: 34303265.
71. Bruckert E, Caprio S, Wiegman A, et al. Efficacy and Safety of Alirocumab in Children and Adolescents With Homozygous Familial Hypercholesterolemia: Phase 3, Multinational Open-Label Study. Arterioscler Thromb Vasc Biol. 2022; 42(12): 1447–1457, doi: 10.1161/ATVBAHA.122.317793, indexed in Pubmed: 36325897.
72. Gaudet D, Ruzza A, Bridges I, et al. Cognitive function with evolocumab in pediatric heterozygous familial hypercholesterolemia. J Clin Lipidol. 2022; 16(5): 676–684, doi: 10.1016/j.jacl.2022.07.005, indexed in Pubmed: 36210291.