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Efficacy and safety of inclisiran versus PCSK9 inhibitor versus statin plus ezetimibe therapy in hyperlipidemia: a systematic review and network meta-analysis

Shengxuan Zhang[1], Lei Sun[2], Xinyu Xu[3], Yanling Zhang[1] and Qilan Chen[1*]

Objective Hyperlipidemia plays a crucial role in increasing the risk of cardiovascular diseases such as atherosclerosis. Recent studies have established that inclisiran positively influences lipid regulation. Nevertheless, its effectiveness in comparison to conventional treatments is still questionable. Hence, a methodical assessment of its effectiveness and safety is required. This research evaluates the efficacy and safety of inclisiran, PCSK9 inhibitors, and the combination of statins with ezetimibe in the treatment of hyperlipidemia via a network meta-analysis of randomized controlled trials (RCTs).

Methods We performed an extensive search of English-language publications in the PubMed, Medline, Embase, and Cochrane Library databases until April 2024. We conducted a web-based meta-analysis and reported in accordance with the guidelines. We selected the percentage change in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) as efficacy evaluation metrics and the incidence of adverse events as safety evaluation metrics for analysis and comparison.

Result We incorporated 33 studies involving 23,375 patients, evaluating three interventions regarding their effects on LDL-C, TC, TG, HDL-C, and adverse events. All treatments improved metrics over placebo. Inclisiran significantly reduced LDL-C compared to statins (mean −15.21, 95% CI [-25.19, -5.23]) but showed no significant difference from statin + ezetimibe. Surface under the cumulative ranking curve (SUCRA) rankings placed inclisiran highest for LDL-C reduction (26.2%). The combination of statin and ezetimibe was the most efficacious for triglyceride reduction (mean 17.2, 95% CI [10.22, 24.19]; mean 15.61, 95% CI [16.87, 24.35]). The safety profiles were comparable across treatments.

Conclusion Inclisiran with its superior LDL-C reduction and low frequency of administration, appears promising for hyperlipidemia treatment, particularly for patients with adherence issues or side effects from other medications.

Systematic review registration CRD42024550852

Keywords Inclisiran, PCSK9 inhibitor, Statin, Ezetimibe, Hyperlipidemia, Network meta-analysis, A systematic review

*Correspondence:
Qilan Chen
cql13588750941@qq.com
[1]Department of Cardiology, Hangzhou Traditional Chinese Medicine Hospital, Affiliated to Zhejiang Chinese Medical University, No.453 Sports Stadium Road 310007, Hangzhou, Zhejiang Province 310007, China
[2]Department of Gastroenterology, Hangzhou Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang Province 310007, China
[3]Department of Medical Oncology, Hangzhou Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang Province 310007, China

Introduction

According to figures from the World Health Organization, cardiovascular disease was the primary cause of mortality worldwide, accounting for around 31% of all deaths. The majority are attributable to atherosclerosis [1, 2]. Hyperlipidemia is a dyslipidemic disorder. It is suggested that it may cause atherosclerosis and increase the risk of cardiovascular events, making the regulation of abnormal blood lipids essential [3]. Data from a study showed about 53% of adults have elevated low-density lipoprotein cholesterol (LDL-C), but less than 50% of them receive lipid-lowering therapy, and only 35% of them can be effectively controlled; these patients have a 2-fold risk of atherosclerotic cardiovascular disease (ASCVD) compared with lipid-achieving populations [4].

Currently, lipids can be regulated through dietary modifications, physical exercise, and pharmacological interventions. Statins are well-known hypolipidemic drugs [5], which can reduce LDL-C about 20–65% by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [6, 7]. A meta-analysis showed that a 39 mg/dL reduction in LDL-C reduced the risk of cardiovascular events by about 24% in patients who took statins [8]. Ezetimibe lowers LDL-C by reducing intestinal cholesterol absorption, and multiple clinical studies showed that it has better efficacy when it combines with statins [9–11]. So previous studies and guidelines recommend that we can add ezetimibe to statin therapy when blood lipids are poorly controlled. Nonetheless, the administration of traditional statins is linked to negative effects, such as drug-induced myopathy and hepatotoxicity [12]. Furthermore, statin intolerance is observed in approximately 5–30% of patients [13]. There is a necessity to identify more suitable pharmacological agents to regulate lipid levels in this patient population.

From a clinical perspective, it has been discovered that levels of PCSK9 increase within a few hours of cardiovascular events, such as acute coronary syndromes [14]. PCSK9, a protein involved in the regulation of LDL receptor degradation in hepatocyte cell membranes [14]. and it plays a crucial role in LDL-C reduction. Consequently, various drugs targeting the reduction of PCSK9 levels have been developed, including PCSK9 inhibitors and inclisiran. The traditional PCSK9 inhibitors include alirocumab and evolocumab. They offer convenience relative to oral statin medications and can typically be administered as bi-weekly or monthly injections based on LDL-C levels. They facilitate LDL-C clearance by inhibiting the interaction of the PCSK9 protein with the LDL receptor, consequently augmenting the quantity of LDL receptors in the liver, and they may also diminish the incidence of cardiovascular risk events [2, 15–18]. They have shown remarkable results in lowering cholesterol and are particularly suitable for patients whose cholesterol levels cannot be effectively controlled by statins or other conventional treatments. However, they are more expensive and have side effects such as injection site reactions (e.g., redness, swelling, pain), flu-like symptoms (e.g., fatigue, headache), and symptoms of upper respiratory tract infections, which need to be taken into consideration when using them clinically.

In recent years, Inclisiran, a small interfering RNA, has gained prominence as a subcutaneously administered medication [19]. Inclisiran reduces PCSK9 levels through an RNA interference mechanism, significantly lowering LDL-C levels, often by more than 50% [20–23]. Pharmacophore studies indicate that PCSK9 exhibits a stronger interaction with LDL-C [24]. Thus, inclisiran and PCSK9 inhibitors may demonstrate enhanced efficacy relative to conventional statin therapy. Recent studies demonstrate that inclisiran is well tolerated over the long term, showing a diminished risk of myopathy and hepatotoxicity relative to conventional statin therapy [25]. Additionally, inclisiran has been shown to achieve a more rapid LDL-C reduction compared to conventional therapies [26]. Adverse reactions to inclisiran are associated with injection site reactions. Inclisiran is usually administered once every 6 months, and its adverse effects are primarily related to injection site reactions. Due to its long-lasting efficacy and less frequent administration, inclisiran may have advantages over PCSK9 inhibitors.

Since statin + ezetimibe therapy has better efficacy than single statin therapy, and inclisiran is the most recently studied drug, currently, we lack the comparisons of the overall efficacy of statin + ezetimibe therapy, PCSK9 inhibitors, and inclisiran. To compare the efficacy and safety of statin plus ezetimibe therapy, PCSK9 inhibitors, and inclisiran in treating hyperlipidemia, we identified these three interventions and conducted a review of pertinent randomized clinical trials to assess their efficacy and safety through network meta-analysis (NMA).

Materials and methods

Registration

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the following registration number: CRD42024550852.

Search strategy and data extraction

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards diligently [27, 28]. A thorough investigation was carried out in the databases PubMed, Medline, Embase, and Cochrane Library till April 2024. The search strategy employed specific MESH terms, including "inclisiran," "PCSK9," "statin," "ezetimibe," "hyperlipidemia," and

"randomized controlled trial (RCTs)," to ensure the inclusion of all relevant literature.

Furthermore, we meticulously examined numerous references from the acquired publications and proactively sought additional relevant materials, including research reports and conference proceedings. The search parameters were confined to randomized controlled trials involving human subjects. Duplicates were eliminated based on title, author, year, and abstract utilizing EndNote X21. Following the review of the title and abstract, two authors (SX and L) conducted a preliminary assessment according to the established inclusion and exclusion criteria for this paper. The complete text of the selected literature was subsequently downloaded and examined for a secondary evaluation. When the two independent reviewers disagreed regarding the literature's eligibility, an additional researcher (YL) was consulted. Data and information on eligible RCTs were extracted independently by 2 researchers based on the screening results: first author, year of publication, sample size, interventions in the study group, interventions in the control group, outcome indicators, and number of adverse events. And another researcher (XY) was checked for verification at the end of the extraction. SX and L evaluated the risk of bias and quality of included trials using the Cochrane Guidelines [29]. Disagreements between the reviewers were resolved by the third author (QL).

Study selection

We employed the PICOS (Population, Interventions, Comparisons, Outcomes, Study designs) framework to define the eligibility criteria. The studies incorporated in the review satisfied the subsequent criteria: (1) Patients aged≥18 years with LDL-C≥2.6 mmol/L, or other patients who meet the criteria set by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guidelines, with no restriction on gender or ethnicity, (2)If the patient is on lipid-lowering therapy they will need to undergo a drug elution period, (3) The intervention measures included Inclisiran, PCSK9 inhibitors, or statin plus ezetimibe, with the control group receiving a placebo, with no restrictions on specific varieties and dosages of various types of drugs, (4) Outcome measures included LDL-C, TC, TG, HDL-C, and adverse events, and (5) The study was a RCT. The exclusion criteria were as follows: (1) The subjects were not human, (2) The article was a review or another type of non-RCT study, (3) Pregnant or breastfeeding patients, individuals on medications that could influence the results, and other conditions deemed by the investigator to potentially impact the trial.,(4) The study did not include any of the indicators LDL-C, TC, TG, HDL-C, or adverse events, and (5) The data were incomplete or could not be extracted.

Outcome measures

Our network meta-analysis (NMA) distinguishes itself from conventional meta-analyses by integrating and evaluating data from multiple randomized controlled trials (RCTs). The evaluated outcome measures comprised percentage alterations in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), as well as the frequency of adverse events.

Statistical analysis

We employed Stata 17.0 software to evaluate the extracted continuous variables for NMA, producing the standardized mean difference (SMD) together with 95% confidence intervals (CI) or the odds ratio (OR) with 95% CI. Statistical heterogeneity was assessed, and a fixed-effects model was applied if $I^2 < 50\%$ and $p > 0.01$. Otherwise, a random-effects model was employed. Publication bias and small-sample effects were evaluated using funnel plots. Results were ranked based on the surface under the cumulative ranking curve (SUCRA), with higher SUCRA values signifying superior potential therapeutic effects. A matrix was created to evaluate all interventions and ascertain whether the SUCRA differences between intervention pairs were statistically significant. Consistency and inconsistency of these relationships were evaluated to enhance the stability of the results. Statistical significance was set at $P<0.05$.

Results

Literature search and included studies

According to the search methodology, 6,594 studies were extracted from the three databases. Following the elimination of duplicate articles and the screening of titles and abstracts, 343 studies were retained; subsequently, upon full-text evaluation, 310 studies were excluded. There were 33 eligible studies that included 23,375 patients meeting the inclusion criteria for hyperlipidemia. (Figure1)Information on the included studies is listed in Table 1. (Table 1)

Network plots of eligible comparisons

Figure 2 demonstrates that the placebo group serves as the primary control group across all trials, with some studies featuring pairwise comparisons among various intervention measures. The forest plot for LDL-C (Figure A) comprises 7 nodes, enabling 9 comparisons. The forest plot for HDL-C (Figure B) comprises 6 nodes, enabling 8 comparisons. The forest plot for TC (Figure C) comprises 6 nodes, enabling 8 comparisons. The forest plot for TG (Figure D) comprises 6 nodes, facilitating 8 comparisons. Finally, the forest plot for safety evaluation (Figure E) comprises 7 nodes, enabling 10 comparisons.

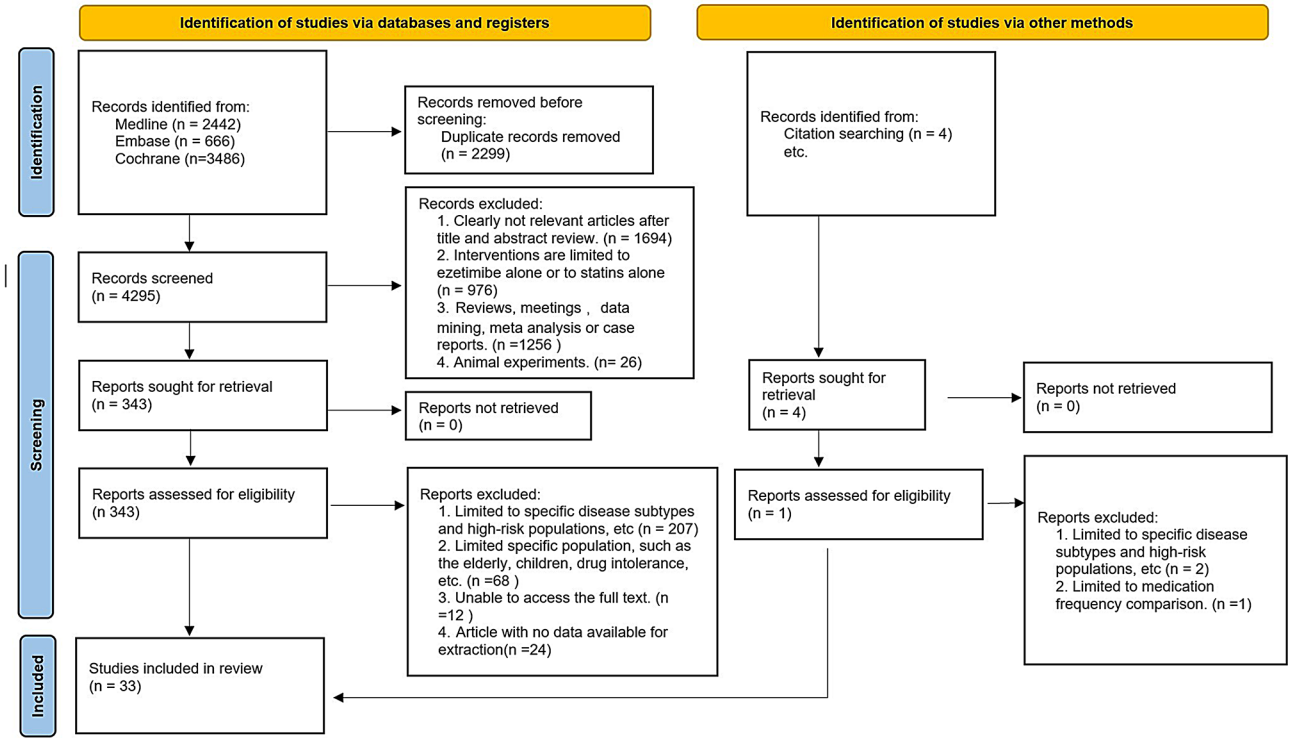

Fig. 1 PRISMA flow diagram for search and selection of eligible studies included in the network meta-analysis

Efficacy evaluation

The paired meta-analysis results (Fig. 3) indicate significant reductions in LDL-C with the three intervention measures: Inclisiran, PCSK9 inhibitors, and statin plus ezetimibe therapy, compared to the placebo group (mean −49.95, 95% CI [-55.60, -40.30]; mean −44.10, 95% CI [-55.17, -33.04]; mean −45.83, 95% CI [-52.52, -39.41]). However, no statistically significant differences were observed among the three intervention measures (Fig. 3A). For HDL-C and TC, all three interventions showed improvements over the placebo group, yet no significant differences were found among them. Regarding TG, all three interventions demonstrated improvements compared to the placebo, with the combination of statin and ezetimibe therapy achieving statistical significance over PCSK9 inhibitors and Inclisiran (mean 17.2, 95% CI [10.22, 24.19]; mean 15.61, 95% CI [16.87, 24.35]). While Inclisiran exhibited marginally superior performance compared to PCSK9 inhibitors, the difference lacked statistical significance (Fig. 3B).

The assessment outcomes of all intervention interventions were prioritized using SUCRA probability (Fig. 4). It can be observed that the most effective treatment for reducing LDL-C levels is PCSK9 inhibitor+ezetimibe therapy (55.4%). Among the three intervention measures compared, Inclisiran ranked the highest (26.2%), followed by PCSK9 inhibitors (11%), and then statin plus ezetimibe therapy (7.4%) (Fig. 4A). For increasing HDL-C levels, the most effective treatment is statin plus ezetimibe therapy (65.4%), followed by PCSK9 inhibitors (27.9%), and then Inclisiran (25.6%), with the efficacy curves of PCSK9 inhibitors and Inclisiran being remarkably close (Fig. 4B). The most effective treatment for reducing TC levels is the combination of statin and ezetimibe therapy, which achieves a success rate of 91.8%. This is followed by PCSK9 inhibitors at 5.1%, and Inclisiran at 3.1% (Fig. 4C). The interventions are ranked according to their effectiveness in reducing TG levels as follows: statin plus ezetimibe therapy, Inclisiran, ezetimibe, and PCSK9 inhibitors (Fig. 4D).

Safety evaluation

A pairwise meta-analysis was performed to assess the safety of the intervention measures. No statistically significant differences were observed between any intervention group and the placebo group, as illustrated in Fig. 5A. The ranking of safety outcomes was as follows: PCSK9 inhibitor plus ezetimibe>statin plus ezetimibe>statin>Inclisiran>PCSK9 inhibitors>ezetimibe. (Fig. 5B) The slight superiority of inclisiran compared to PCSK9 inhibitors may be attributable to its less frequent dosing regimen. Individually, PCSK9 inhibitor and ezetimibe demonstrate suboptimal safety profiles; however, their combination confers an enhanced safety profile. This observation can be elucidated by the limited number of studies evaluating this metric, and in certain

Table 1 Characteristics of studies used for analysis

Study	year	Treatment	*N*	Age	Gender	Baseline, mean(SD), (mg/dL), (*mmol/L)	Criteria	Duration
				Mean(SD)	(% female)			
Davidson, M. H, et al.	2002	Ezetimibe + Statin	274	57.6 ± 14	54	LDL-C 176.3(19.9), HDL-C 50.4(12.2), TG 178.8(65.1)	%Change of HDL-C, TG and safety	12w
		Statin	263	56.4 ± 15.5	58	LDL-C 178.5(20.0), HDL-C 51.0(10.9), TG 168.7(59.8)		12w
		Ezetimibe	61	60.3 ± 12.25	61	LDL-C 181.3(23.0), HDL-C 51.0(11.5), TG 190.3(68.2)		12w
		Placebo	70	58.8 ± 14.75	39	LDL-C 177.4(21.7), HDL-C 52.3(12.1), TG 170.9(68.5)		12w
Gagné, C, et al.	2002	Ezetimibe + Statin	379	60	41	LDL-C 138(42.83), TC 218(44.78), TG 136(79.82), HDL-C 49(11.68)	%Change of LDL-C, TC, TG, HDL-C	8w
		Statin	390	60	43	LDL-C 139(39.5), TC 219(41.47), TG 137(75.04), HDL-C 50(11.85)		8w
Boris Kerzner, et al.	2003	Ezetimibe + Statin	192	57 ± 11	55	LDL-C 176(13.86), TC 262(27.71), TG 171(55.43), HDL-C 50(13.86)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Statin	220	56 ± 12	60	LDL-C 178(14.83), TC 265(29.66), TG 178(59.33), HDL-C 51(14.83)		12w
		Ezetimibe	72	55 ± 11	57	LDL-C 178(16.97), TC 264(25.46), TG 170(59.40), HDL-C 51(8.49)		12w
		Placebo	64	58 ± 12	63	LDL-C 178(24), TC 266(24), TG 168(64), HDL-C 54(16)		12w
Christie M. Ballantyne, et al.	2003	Ezetimibe + Statin	255	58.7(11.4)	58	*: LDL-C 4.65(0.64), TC 6.91(0.64), TG 1.9, HDL-C 1.31(0.32)	%Change of TC, HDL-C and safety	12w
		Statin	248	57.8(11.7)	62	*: LDL-C 4.65(0.63), TC 6.95(0.63), TG 1.7, HDL-C 1.39(0.31)		12w
		Ezetimibe	65	56.7(11.7)	55	*: LDL-C 4.53(0.56), TC 6.7(0.73), TG 1.6, HDL-C 1.31(0.32)		12w
		Placebo	60	56.9(12.1)	52	*: LDL-C 4.6(0.54), TC 6.77(0.70), TG 1.6, HDL-C 1.30(0.31)		12w
Lorenzo Melani, et al.	2003	Ezetimibe + Statin	204	56.9(16.5)	59	*: LDL-C 4.6(0.5), TG 2.0(0.7), HDL-C 1.30(0.3)	%Change of LDL-C, TG, HDL-C and safety	12w
		Statin	205	55.1(15.25)	51	*: LDL-C 4.6(0.6), TG 2.0(0.7), HDL-C 1.30(0.3)		12w
		Ezetimibe	64	52(12.25)	64	*: LDL-C 4.6(0.6), TG 2.0(0.7), HDL-C 1.30(0.3)		12w
		Placebo	65	53.4(11)	52	*: LDL-C 4.6(0.5), TG 1.8(0.7), HDL-C 1.30(0.3)		12w
ANNE C. GOLDBERG, et al.	2004	Ezetimibe + Statin	353		52	LDL-C 175(27), TC 260(30), TG 169(93), HDL-C 51(13)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Statin	349		52	LDL-C 175(25), TC 259(30), TG 167(89), HDL-C 49(12)		12w
		Ezetimibe	92		62	LDL-C 176(26), TC 262(30), TG 163(104), HDL-C 51(13)		12w
		Placebo	93		59	LDL-C 174(28), TC 258(32), TG 162(83), HDL-C 50(12)		12w
C.M. BALLANTYNE, et al.	2004	Ezetimibe + Statin	201	57.6(15)	61	*: LDL-C 4.7(0.6), TC 6.9(0.7), TG 1.8(0.74), HDL-C 1.4(0.4)	%Change of LDL-C, TC, TG, HDL-C and safety	6w
		Statin	45	58.5(10.5)	49	*: LDL-C 4.8(0.6), TC 7.0(0.7), TG 1.8(0.74), HDL-C 1.3(0.3)		6w

Table 1 (continued)

Study	year	Treatment	*N*	Age	Gender	Baseline, mean(SD), (mg/dL), (*mmol/L)	Criteria	Duration
				Mean(SD)	(% female)			
Harold E. Bays, et al.	2004	Ezetimibe + Statin	609	56.4(10.6)	51.4	LDL-C 176.2(24.8), TC 260.8(28), TG 153.3(83.3), HDL-C 51.8(13)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Statin	622	54.9(11.2)	50.6	LDL-C 177.5(25.3), TC 261.7(28.7), TG 155.3(75.3), HDL-C 51(12.3)		12w
		Ezetimibe	149	55.5(11.0)	54.4	LDL-C 179.9(23.1), TC 264.5(26.3), TG 145.5(79.1), HDL-C 52.4(12.8)		12w
		Placebo	148	56.0(10.8)	56.1	LDL-C 177.9(22.8), TC 261.6(28.4), TG 142.8(62.6), HDL-C 52.9(13.2)		12w
Luis Masana, et al.	2005	Ezetimibe + Statin	355	59(15.5)	43	LDL-C 136.6(47.3), TC 216(49), TG 131(4.1), HDL-C 50.1(11.9)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Statin	78	61(13.75)	45	LDL-C 131.4(45.6), TC 211.3(48.6), TG 128(8.4), HDL-C 51(13.4)		12w
Alberico L. Catapano, et al.	2006	Ezetimibe + Statin	1427	55.67(10.28)	52.49	145 ≤ LDLC < 160:498(34.9%); 160 ≤ LDLC < 190:635(44.5%); LDLC > 190:345(24.28%)	%Change of LDL-C and safety	6w
		Statin	1428	55.6(10.4)	56.3	145 ≤ LDLC < 160:500(35.01%);160 ≤ LDLC < 190 :635(44.48%);LDLC > 190:346(24.23%)		6w
Roxanne A. Rodney, et al.	2006	Ezetimibe + Statin	124	55.2(11.6)	61	LDL-C 176.5(23.2), TC 256.3(26.8), TG 124.5(60.0), HDL-C 53.2(13.4)	safety	12w
		Statin	123	53.7(11.5)	62	LDL-C 174.7(23.3), TC 253.3(27), TG 125.5(58.6), HDL-C 50.2(13.4)		12w
L. Ose, et al.	2007	Ezetimibe + Statin	544	56(14.5)	54	*: LDL-C 4.6(0.6), TC 6.8(0.7), TG 1.7(0.9), HDL-C 1.3(0.3)	%Change of LDL-C, TC, TG, HDL-C and safety	14w
		Statin	560	55(15.25)	52	*: LDL-C 4.6(0.6), TC 6.8(0.7), TG 1.7(0.9), HDL-C 1.3(0.3)		14w
Pinakini K. Shankar, et al.	2007	Ezetimibe + Statin	114	52.19(12.2)	60	LDL-C 130.5(40.3), TC 264.1(84.9), TG 236.3(128.6), HDL-C 41.9(7.7)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Statin	116	51.54(10.1)	61	LDL-C 125.5(35.3), TC 258.9(69.5), TG 227.2(146.8), HDL-C 41.7(7.1)		12w
Harold Bays, et al.	2008	Ezetimibe + Statin	539	56.7(14.5)	53	LDL-C 175.1, TC 260.7, TG 163.8, HDL-C 50.7	safety	48w
		Statin	229	55.4(14.25)	48	LDL-C 175.8, TC 259.7, TG 169, HDL-C 48.4		48w
John Strony(1), et al.	2008	Ezetimibe + Statin	359	57.7(11.8)	58	LDL-C 178.4(19.9), TC 264.5(23.7), TG 175.3(59.9), HDL-C 51.1(11.9)	%Change of LDL-C, TC, HDL-C and safety	12 m
		Statin	436	55.7(11.7)	56	LDL-C 178.3(21.7), TC 264.4.5(25.9), TG 175.4(61.5), HDL-C 51.1(11.5)		12 m
John Strony(2), et al.	2008	Ezetimibe + Statin	87	56.4(11.9)	49	LDL-C 178.1(23.8), TC 262.3(29.8), TG 178.7(68.4), HDL-C 48.6(11.8)	%Change of LDL-C, TC, HDL-C and safety	12 m
		Statin	22	60.7(8.4)	64	LDL-C 176.2(23.9), TC 264.0(24.9), TG 177.0(59.9), HDL-C 52.4(10.3)		12 m
Luis A. Alvarez-Sala, et al.	2008	Ezetimibe + Statin	38	50.8(13.5)	52.6	*: LDL-C 5.1(0.9), TC 7.3(1.1), TG 1.7(0.3), HDL-C 1.5(0.5)	safety	12w

Table 1 (continued)

Study	year	Treatment	*N*	Age	Gender	Baseline, mean(SD), (mg/dL), (*mmol/L)	Criteria	Duration
				Mean(SD)	(% female)			
		Statin	44	49.3(10.6)	59.1	*: LDL-C 5.6(1.5), TC 7.7(1.6), TG 1.6(0.7), HDL-C 1.5(0.4)		12w
Chih-Chieh Yu, et al.	2012	Ezetimibe + Statin	42	61.2(10.5)	58.6	LDL-C 144.6(45.8), TC 213.6(48.4), TG 140.3(59.7), HDL-C 48.4(9.1)	safety	8w
		Statin	41	54.2(10.9)	52.9	LDL-C 130.9(19.4), TC 207.3(28.8), TG 158.5(68.1), HDL-C 52.5(11.9)		8w
Dirk J. Blom, et al.	2014	PCSK9 inhibitor	599	55.9(10.8)	51.6	LDL-C104.2(22.1)	safety	52w
		Placebo	302	56.7(10.1)	53.6	LDL-C104.0(21.6)		52w
Michael J. Koren, et al.	2014	Ezetimibe	154	53.5(12.01)	68.18	LDL-C 143.5(23.43), TG 115(52.85), HDL-C 56.5(18.3)	safety	12w
		Placebo	154	53.5(10.5)	73.38	LDL-C 142.3(22.06), TG 116.06(69.43), HDL-C 55.48(21.95)		12w
		PCSK9 inhibitor	306	53(13.02)	66.99	LDL-C 143(22.49), TG 115.5(56.8), HDL-C 55(15.33)		12w
Eli M Roth, et al.	2015	PCSK9 inhibitor + Ezetimibe	52	60.8(4.6)	46.2	LDL-C 141.2(27.1), TC 221.7(33.7), TG 119(47.4), HDL-C 54.3(16.1)	%Change of LDL-C and safety	24w
		Ezetimibe	51	59.6(5.3)	47.1	LDL-C 138.3(24.5), TC 223.9(30.2), TG 117(49.63), HDL-C 59.9(19.2)		24w
Kausik K. Ray, et al.	2017	Inclisiran	369	63.56(11.04)	32.79	LDL-C 129.47(53.39), TC 211.5(62.06), TG 127.37(68.6), HDL-C 48.81(13.53)	%Change of LDL-C, TC, HDL-C and safety	180d
		Placebo	127	62.39(10.84)	38.58	LDL-C 126.89(47.85), TC 208.04(56.62), TG 130.86(58.98), HDL-C 50.53(14.83)		180d
Woohyeun Kim	2018	Ezetimibe + Statin	188	62.06(9.03)	44.1	LDL-C 160.61(30.97), TC 228.78(34.85), TG 153.34(65.88), HDL-C 50.69(13.52)	%Change of LDL-C, TC, TG, HDL-C	8w
		Statin	187	61.26(9.22)	41.2	LDL-C 160.03(31.19), TC 227.51(34.30), TG 158.17(65.90), HDL-C 48.90(11.29)		8w
Tamio Teramoto	2019	PCSK9 inhibitor	107	63.1(10.1)	38.32	LDL-C 151.72(47.44), TC 238.12(49.88), TG 149.66(25.29), HDL-C 54.7(11.6)	%Change of TC, TG, HDL-C and safety	12w
		Placebo	56	64.6(10.0)	33.9	LDL-C 149.4(32.6), TC 234.4(37.1), TG 150.5(19.88), HDL-C 54.3(10.1)		12w
Kausik K. Ray, et al.	2020	Inclisiran	1591	65.56(8.63)	30	LDL-C 105.87(40.47), TC 184.01(47.28), TG 131.07(63.45), HDL-C 48.18(15)	safety	540d
		Placebo	1587	65.24(8.80)	28.89	LDL-C 104.24(36.69), TC 181.97(43.2), TG 132.05(62.63), HDL-C 47.63(14.2)		540d
Xuan Jin, et al.	2020	PCSK9 inhibitor	15	72.9(6.5)	6.7	LDL-C 101.8(20), TC 179.5(27.8), TG 145.7(58.1), HDL-C 48.7(12.2)	safety	24w
		Placebo	14	64.8(7.3)	21.4	LDL-C 93.4(37.9), TC 164.9(38.4), TG 121.4(58), HDL-C 44.1(11)		24w
R. Scott Wright, et al.	2021	Inclisiran	1833	64.1(9.98)	33.1	LDL-C 111.9(44.9), TC 190.1(50.7), HDL-C 48.6(15)	%Change of LDL-C, TC and safety	540d
		Placebo	1822	63.9(9.87)	31.9	LDL-C 110.8(43.6), TC 188.6(49.3), HDL-C 48.0(14.1)		540d
F Raal, et al.	2022	Inclisiran	148	58.3(10.3)	41.2	*: LDL-C 3.6(1.4), TC 5.6(1.6)	%Change of LDL-C and safety	540d
		Placebo	150	58.9(11.5)	46	*: LDL-C 3.6(1.7) ,TC 5.7(1.8)		540d
Hong Tan, et al.	2022	PCSK9 inhibitor	159	61.05(10.17)	35.85	LDL-C 114.61(34), TC 189.8(36.42), TG 128.12(48.19), HDL-C 47.95(13.17)	%Change of TC and safety	12w

Table 1 (continued)

Study	year	Treatment	*N*	Age	Gender	Baseline, mean(SD), (mg/dL), (*mmol/L)	Criteria	Duration
				Mean(SD)	(% female)			
		Placebo	82	58.6(10.33)	25.61	LDL-C 119(35.72), TC 189(40.63), TG 119(43.48), HDL-C 43.4(10.28)		12w
Ming-Ting Chou, et al.	2022	Ezetimibe + Statin	128	53.9(12.4)	57	LDL-C 172.7(26.7), TC 242.6(29.9), TG 144.9(62.1), HDL-C 54.8(16.0)	safety	12w
		Statin	132	51.7(11.4)	53.8	LDL-C 174.9.7(27.2), TC 244.5(30.2), TG 145.5(61.6), HDL-C 54.3(13.7)		12w
		Ezetimibe	128	55.8(11.3)	60.2	LDL-C 172.7(25.8), TC 241.2(28.9), TG 148.1(60.6), HDL-C 53.4(12.2)		12w
Mingtong Xu, et al.	2022	PCSK9 inhibitor	91			*: LDL-C 3.57(0.83), TC 5.26(0.25)	%Change of TC and safety	24w
		Placebo	19			*: LDL-C 3.36(0.928), TC 5.29(0.61)		24w
Zhu Luo, et al.	2023	Inclisiran	29	61.05(9.1)	76.67	LDL-C 126.5(21.99), TG 159.2(89.22)	%Change of LDL-C	90d
		Placebo	10	57.3(9.59)	60	LDL-C 133(17), TG 159.1(70.6)		90d
Michael J Koren, et al.	2024	PCSK9 inhibitor	213	64.6(9.13)	30.5	*: LDL-C 2.7(0.76), TC 4.75(1.06), TG 1.6(0.96), HDL-C 1.28(0.37)	%Change of LDL-C, TC, TG, HDL-C and safety	12w
		Placebo	54	63.1(8.6)	32	*: LDL-C 2.5(0.9), TC 4.6(1.1), TG 1.7(0.9), HDL-C 1.2(0.3)		12w

Note * The unit of measurement is mmol/L; d:day; w:week; m:month

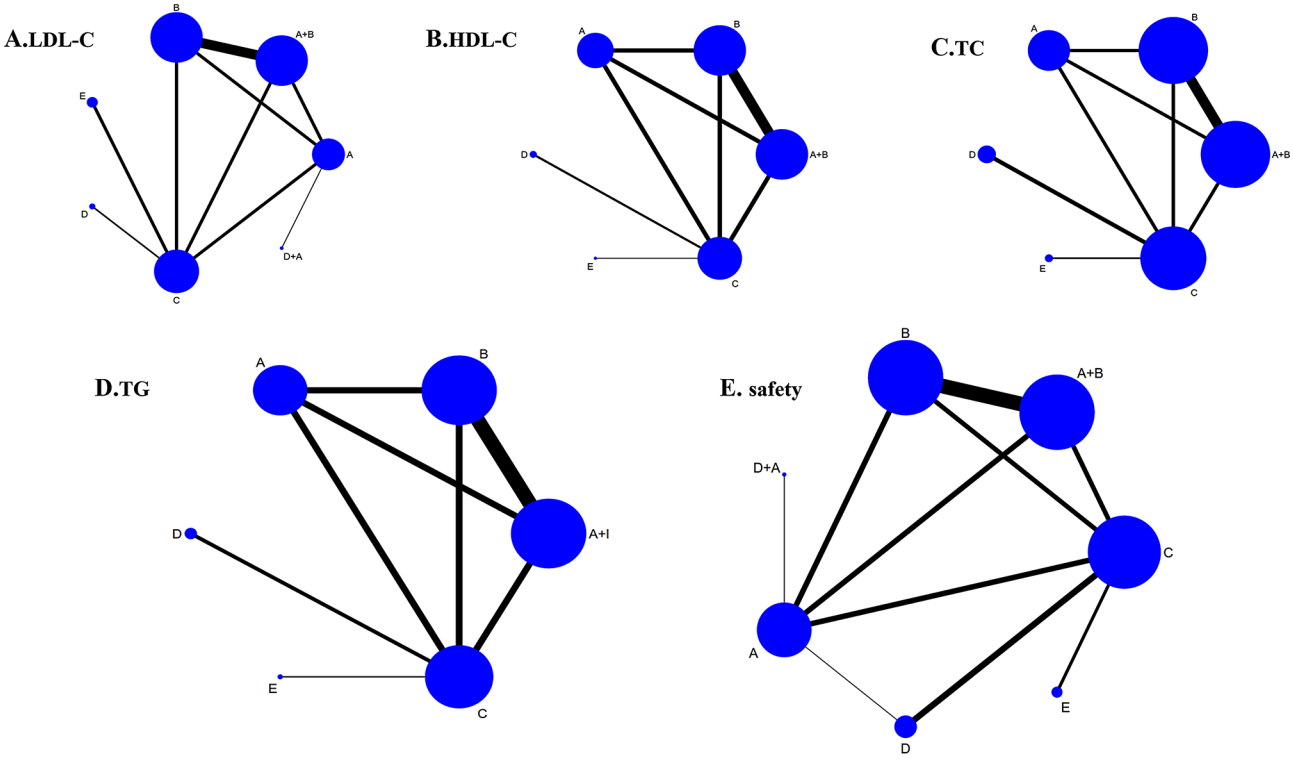

Fig. 2 Network of eligible comparisons for all treatments included in the analyses. Note (**A**) LDL-C, (**B**) HDL-C, (**C**) TC, (**D**) TG, (**E**) safety

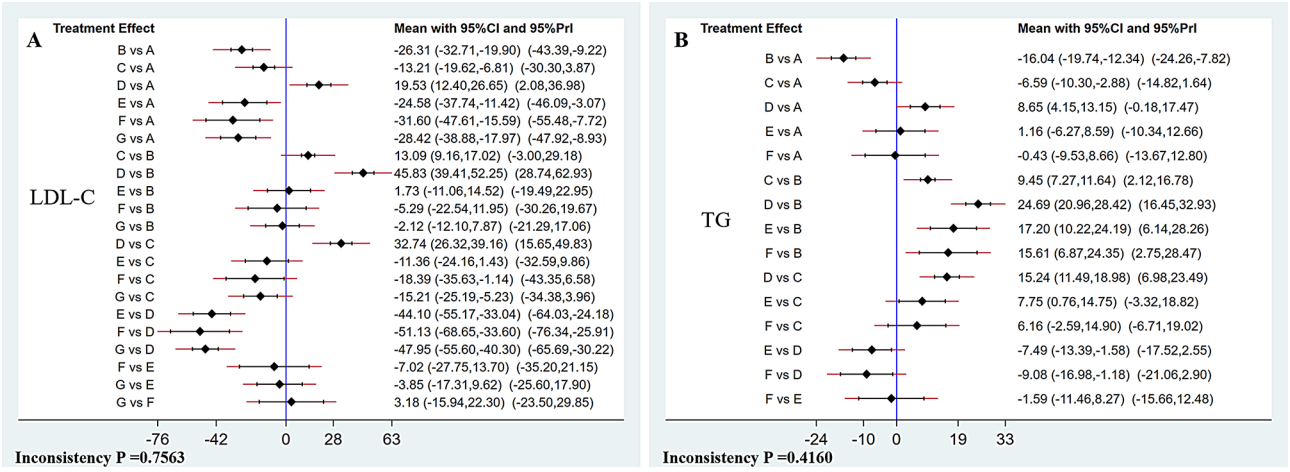

Fig. 3 The forest plot comparing various intervention measures in improving LDL-C and TG. (**A**) A: Ezetimibe, B: Ezetimibe + statin, C: statin D: Placebo, E: PCSK9 inhibitor, F: PCSK9 inhibitor + Ezetimibe, G: Inclisiran. (**B**)A: Ezetimibe, B: Ezetimibe + statin, C: statin D: Placebo, E: PCSK9 inhibitor, F: Inclisiran

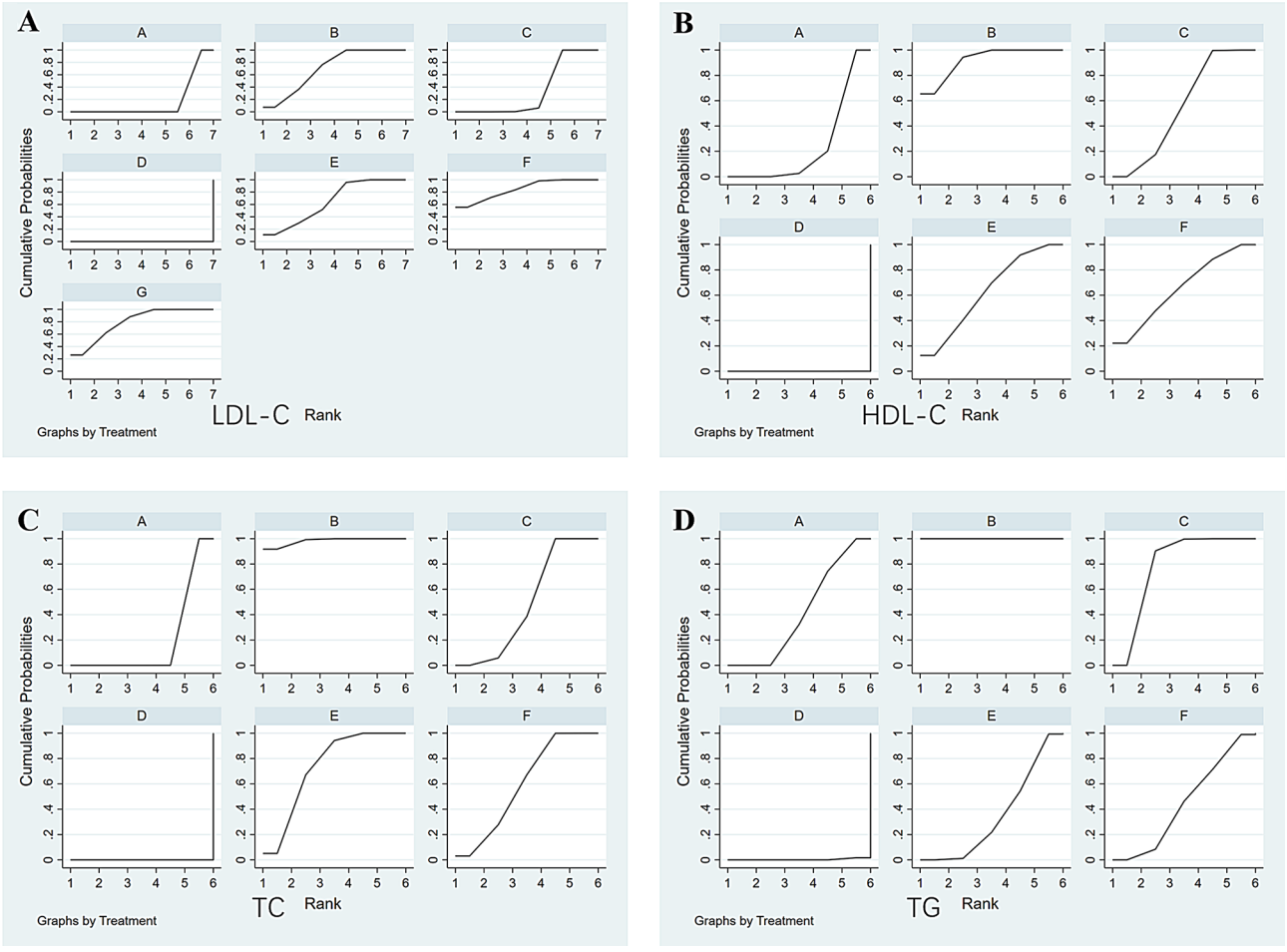

Fig. 4 SUCRA for various intervention measures in improving LDL-C, HDL-C, TC and TG (**A**)A: Ezetimibe, B:Ezetimibe + statin, C: statin D: Placebo, E: PCSK9 inhibitor, F: PCSK9 inhibitor + Ezetimibe, G: Inclisiran (**B**, **C**, **D**)A: Ezetimibe, B:Ezetimibe + statin, C:statin D: Placebo, E: PCSK9 inhibitor, F: Inclisiran

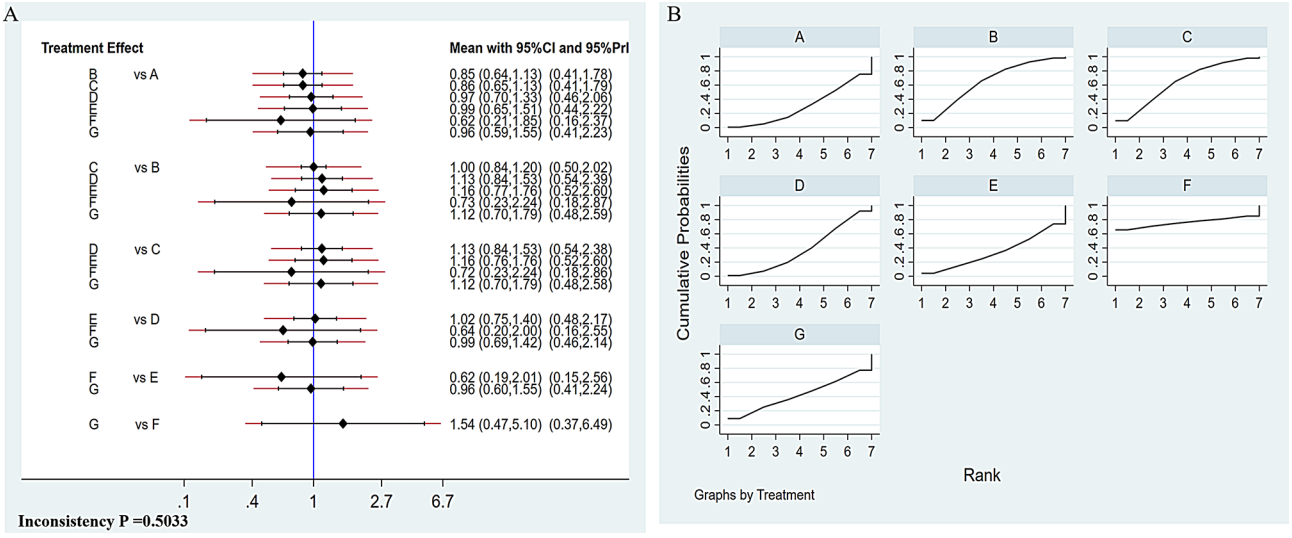

Fig. 5 The forest plot (**A**) and SUCRA (**B**) for various intervention measures in safety (**A**, **B**)A: Ezetimibe, B:Ezetimibe + statin, C:statin D: Placebo, E: PCSK9 inhibitor, F: PCSK9 inhibitor + Ezetimibe, G: Inclisiran

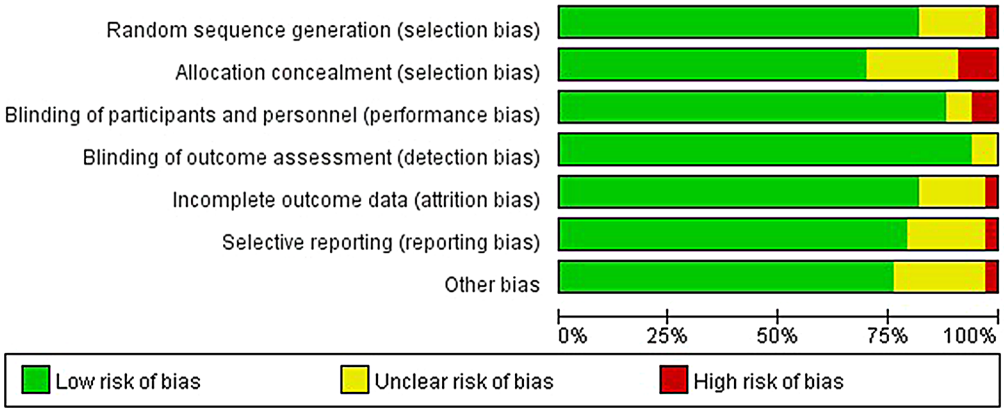

Fig. 6 Risk of bias graph

instances, the safety of this combination is found to be superior. Consequently, this combination offers a relative advantage in populations exhibiting minimal safety discrepancies. However, further clinical data are necessary to validate this finding.

Quality assessment

An RCT with a 3% bias risk was found to have inadequate sequence generation. In terms of allocation concealment, a significant majority of trials (69.7%) employed effective methods such as using opaque envelopes or central randomization systems to ensure a minimal risk of bias. Two (6.1%) trials did not mention whether participants and personnel were blinded or not, while one (3%) was not blinded to outcome assessment. In all RTCs, there was only one instance each of selective reporting bias and incomplete outcome data. In all included trials, other biases were not clearly defined. As a result, the overall quality of the included articles is elevated. Figures 6 and 7 illustrate the risk of bias graph and the risk of bias summary for the studies selected.

Sensitivity and publication bias

Sensitivity analysis revealed that the exclusion of any single study or subgroup of studies with specific characteristics had an insignificant effect on the SMD and its 95% CI. Egger's regression test and Begg's adjusted rank correlation test did not indicate significant publication bias.

Discussion

Recent studies have shown that the maximum reduction in LDL-C can let people benefit from ASCVD continuously without increasing significant adverse events [30]. Therefore, it is essential to identify the most effective medication to rapidly reduce LDL-C levels. This study compared several current common pharmacological interventions for hyperlipidemia, including traditional statin + ezetimibe therapy, PCSK9 inhibitors, and

Fig. 7 Risk of bias summar

emerging inclisiran. Our findings indicate that inclisiran demonstrates a greater efficacy than statins in reducing LDL-C levels, with the observed difference reaching statistical significance. The SUCRA probability indicated a degree of superiority for inclisiran; however, this advantage did not reach statistical significance when comparing the combination of statin and ezetimibe therapy with PCSK9 inhibitors. The combination of conventional statin therapy with ezetimibe continues to demonstrate greater efficacy in the reduction of TG levels. No statistically significant differences were identified among the three interventions or when compared to the placebo group in terms of safety.

Past research has indicated that inclisiran and PCSK9 inhibitors have comparable impacts on lowering LDL-C levels and mitigating the risk of cardiovascular events [31]. This is like the findings of this study. However, some studies suggested that inclisiran is slightly inferior to PCSK9 inhibitors in lowering LDL-C [32]. This may be due to the difference in the duration of observation, which is usually 12 or 24 weeks for PCSK9 inhibitors and 540 days for inclisiran. PCSK9 inhibitors focus on short-term rapid LDL-C reduction, whereas inclisiran focuses more on long-term maintenance of low LDL-C levels, and the difference in the duration of observation may have an impact on the conclusions drawn. The SUCRA probability outcomes in this study indicated that inclisiran may be the most effective of the three therapies in reducing LDL-C; however, the differences among them are not statistically significant. Recent studies have demonstrated that inclisiran significantly reduces LDL-C levels [25]. Nonetheless, because inclisiran is the most recent medication, there have been fewer studies conducted, whereas traditional therapies have encompassed a larger patient demographic; thus, additional RTCs are necessary to establish a statistically significant difference.

Furthermore, our findings indicate that the combination of PCSK9 inhibitor and ezetimibe medication was more effective in reducing LDL-C levels compared to the three therapies we evaluated, as determined by SUCRA probability. These therapies can lower PCSK9 levels, facilitating the conversion of LDL-C receptors and promoting the internalisation of LDL-C, which reduces plasma LDL-C levels, while simultaneously decreasing intestinal cholesterol absorption. This dual mechanism leads to a more significant decrease in LDL-C.

Previous research has demonstrated that an increased TG parameter not only accelerates the progression of atherosclerosis and raises the likelihood of heart disease [32], but also triggers the onset of diabetes [33]. And many studies have used triglyceride combined with glucose index as an insulin resistance level to evaluate metabolic syndrome [33]. Therefore, controlling TG levels is of great significance for metabolic syndrome patients with dyslipidemia and diabetic insulin resistance. The results of this study suggested that the most effective therapy for lowering TG is still the traditional statin+ezetimibe therapy. This may occur because statins not only decrease LDL-C but also enhance the activity of plasma

lipoprotein lipase (LPL), which facilitates the degradation of triglycerides in very low-density lipoproteins (VLDL) and chyme particles, consequently lowering plasma TG levels. The amalgamation of statins, which inhibit hepatic cholesterol synthesis, and ezetimibe, which diminishes intestinal cholesterol absorption, markedly lowers total cholesterol levels in the body. This complementary mechanism also indirectly reduces VLDL production and TG transport. This synergistic effect not only improves therapeutic efficacy but also reduces statin dosage and potential side effects [34].

To guarantee safety, our evaluation primarily depended on the overall frequency of adverse events. Our investigation determined that the three therapies did not exhibit statistically significant differences in terms of safety compared to the placebo group. Based on previous studies in the literature, the main adverse effects of statin are muscle and liver related problems [13]. According to SUCRA ranking, ezetimibe and statin were slightly less safe when combined than inclisiran and PCSK9 inhibitors. This may be due to competition in metabolic pathways. Many statins are metabolized by the cytochrome P450 (CYP450) enzyme system in the liver, particularly cytochrome P450 3A4(CYP3A4). Ezetimibe is predominantly metabolised by the liver via the glucuronidation pathway. Competition within this metabolic pathway may lead to elevated drug concentrations in the body, thereby increasing the likelihood of adverse effects. Consequently, consistent assessment of liver function and creatine kinase levels, dosage optimisation, and vigilance regarding drug interactions are essential measures to ensure patient safety during statin administration.

A recent 2024 study revealed that the primary negative consequences of PCSK9 are associated with injection site responses and the potential for infection. Moreover, it was more evident in at-risk populations, such as those with ischemic stroke or chronic kidney disease [35]. MK-0616, an oral PCSK9 inhibitor, has emerged as a potential alternative to injectable treatments; however, it is still undergoing clinical trials, and its safety and efficacy require further validation before widespread clinical application. Some studies shown the adverse events of inclisiran were also primarily due to its injection mode. This was like PCSK9 inhibitors, and according to clinical data, injection reactions to inclisiran were mild [36]. Inclisiran, being a novel pharmacological agent, undergoes a trial duration that spans 540 days, and its long-term safety profile has yet to be established.

In a clinical context, it is essential to evaluate the economic ramifications when prescribing medications. Research findings indicate that the combination of statin and ezetimibe therapy exhibits greater economic benefits than PCSK9 inhibitors [37]. This treatment option is cost-effective and suitable for most patients but requires monitoring for adverse effects. PSCK9 inhibitors cost more than statin therapy, but he can lower LDL-C levels more quickly and is given less frequently than statin therapy. Notwithstanding its substantial initial expense, inclisiran's capacity to sustain low LDL-C levels over an extended period and mitigate cardiovascular events may yield long-term economic advantages; however, further research is required to validate this assertion [25].

Considering the results, it is crucial to consider patients' specific requirements and treatment objectives when choosing LDL-C lowering regimens in clinical settings. For initial treatment, statins plus ezetimibe are usually preferred due to their good lipid-lowering effects and cost-effectiveness. In cases where patients exhibit intolerance to statins or are unable to reach the target LDL-C levels, PCSK9 inhibitors offer a robust lipid-lowering effect and are appropriate for individuals requiring prompt and substantial reductions in LDL-C. The predominant PCSK9 inhibitors are alirocumab and evolocumab, both of which can markedly decrease LDL-C levels and diminish the risk of cardiovascular incidents. Alirocumab provides various dosage options, including biweekly injections of 75 mg or 150 mg, accommodating patients who need flexible dosage modifications. Evolocumab offers a monthly injection option, which improves patient compliance. Inclisiran, characterized by its semi-annual injection regimen, is especially advantageous for patients requiring sustained and stable control of LDL-C levels, particularly those exhibiting suboptimal adherence to treatment protocols. The final therapeutic choice should be individualized, considering the patient's clinical background, economic status, and adherence.

Limitations

Firstly, the studies in the network meta-analysis may not be fully comprehensive because we excluded certain groups, like people with hyperlipidemia who also have kidney disease. Secondly, certain studies exhibited the absence of specific indicators or the inability to extract them, resulting in an insufficient depth of analysis. Thirdly, the randomized controlled trials incorporated in this study varied in treatment duration, dosage, and administration frequency. It is possible that some underutilized databases contain literature that satisfies the inclusion criteria, potentially influencing the results.

Conclusion

This study presents a theoretical foundation for the treatment and safety assessment of three approaches to managing hyperlipidemia: statin+ezetimibe therapy, PCSK9 inhibitor, and inclisiran. Inclisiran is believed to have long-term benefits that can help lower the risk of heart problems, making it a good option for reducing LDL cholesterol. Conversely, the combination of statin and

ezetimibe therapy is more cost-effective and efficacious in lowering triglycerides. This study solely examined the differences in efficacy and safety among the three measures, without accounting for additional factors. The dose-response relationship requires further investigation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04321-z.

Supplementary Material 1

Author contributions

S. X. Z. and L. S performed the screening of literature and data analysis. X. Y. X and Y. L. Z examined the literature and data of the studies included. S. X. Z. wrote and revised the manuscript. S. X. Z. and Q. L. C. conceived and designed the study. Q. L. C. received financial support. S. X. Z. and L. S. reviewed the full text and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

This is a systematic review and meta-analysis, ethics approval and consent to participate are not applicable.

Competing interests

The authors declare no competing interests.

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