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# Efficacy and Safety of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors as Adjuvant Treatments for Patients with Hypercholesterolemia Treated with Statin: A Systematic Review and Network Meta-analysis

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**Background:** The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are potent LDL-C lowering agents. However, few head-to-head studies evaluated the efficacy on the lowering in other atherogenic apolipoproteins and safety of PCSK9 inhibitors at different dosages as an add-on statins therapy in hypercholesterolemia patients.

**Methods:** This study is a systematic review and network meta-analysis of randomized control trials to compare the efficacy of lipid reduction and adverse events of PCSK9 inhibitors in statin-treated hypercholesterolemia patients. PubMed, EMBASE, and Cochrane Library databases were searched till April 20, 2021, for randomized controlled trials. Random-effect network meta-analyses were undertaken to compare the differences in the percent reduction in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and lipoprotein (a) [Lp(a)] levels and the risk of AEs among different PCSK9 inhibitors.

**Results:** A total of 22 articles with 42,786 patients were included. The lipid reductions in LDL-C, ApoB, and Lp(a) with add-on PCSK9 inhibitors vs. placebo in statin-treated patients across all trials were 50–63%, 43–52%, and 23–31%, respectively. Evolocumab 140 mg Q2W was ranked the best among all treatment strategies for lowering LDL-C, ApoB, and Lp(a) levels, and the treatment difference was 68.05% (95% confidence interval (CI), 62.43% to 73.67) in LDL-C reduction, 54.95% (95% CI, 49.55% to 60.35%) in ApoB reduction, and 34.25% (95% CI, 27.59% to 40.91%) in Lp(a) reduction compared with the placebo. No significant risk difference of adverse events between PCSK9 inhibitors and placebo was found.

**Conclusion:** PCSK9 inhibitors showed a significant effect on the reduction in LDL-C, ApoB, and Lp(a) levels in statin-treated patients. Evolocumab 140 mg Q2W showed significantly larger degrees of LDL-C, ApoB, and Lp(a) reduction.

**Keywords: PCSK9 inhibitors, add-on therapy, low-density lipoprotein cholesterol, hypercholesterolemia, atherogenic apolipoproteins**

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## INTRODUCTION

Dyslipidemia, especially a high level of low-density lipoprotein cholesterol (LDL-C), has long been a critical risk factor in the development of cardiovascular disease (CVD) (Benn et al., 2007; Stamler and Neaton, 2008; Contois et al., 2009; Mellwig et al., 2017; Abdullah et al., 2018; Andersson et al., 2019; Robinson et al., 2020). A target-driven, lipid-lowering treatment is essential for CVD prevention. Besides LDL-C as the primary lipid target for prevention of CVD, atherogenic (apo) lipoproteins beyond LDL-C, such as apolipoprotein B (ApoB) and lipoprotein (a) [Lp(a)], may account for the residual cardiovascular risks (Hermans and Fruchart, 2010; Dhindsa et al., 2020).

For the population at higher cardiovascular risk, especially those with established CVD, intensive lipid-lowering has come to a consensus. However, failure to attain the lipid treatment target was observed despite evidence-based therapy with maximally tolerated statins (Fiévet and Staels, 2009; Hermans and Fruchart, 2010; Mach et al., 2020). Therefore, in very high–CVD risk patients, add-on statin therapy with other lipid-lowering treatments to reach the lipid level goal (Fiévet and Staels, 2009; Gupta, 2015; Lepor and Kereiakes, 2015), that is, LDL-C less than 70 mg/dl is recommended by the lipid-lowering guidelines (Grundy et al., 2019; Mach et al., 2020).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) facilitates the degradation of the low-density lipoprotein receptor (LDL-R) and hinders the clearance of LDL-C (Everett et al., 2015; Lepor and Kereiakes, 2015; Lloyd-Jones et al., 2016; Grundy et al., 2019). Monoclonal antibodies inhibiting PCSK9 function and small interfering RNA reducing PCSK9 synthesis led to higher hepatic LDL-R expression and lower plasma LDL-C levels. PCSK9 inhibitors and small interfering RNA are recommended for high–CVD risk patients unable to achieve the lipid-lowering target by maximally tolerated oral therapies, including statins and/or ezetimibe (Kosmas et al., 2018; Ray et al., 2020; Macchi et al., 2021).

Two PCSK9 inhibitors, alirocumab and evolocumab, are approved for LDL-C reduction (Everett et al., 2015; Macchi et al., 2021). Clinical trials of both PCSK9 inhibitors demonstrated significant reduction of LDL-C and other atherogenic apolipoproteins, such as apolipoprotein B and Lp(a), which are attributable to the residual cardiovascular risk (Lepor and Kereiakes, 2015). Moreover, evidence has revealed that PCSK9 inhibitors lead to a lower risk of subsequent cardiovascular events by intensive LDL-C lowering (Myers et al., 2019; Sabatine, 2019). The ODYSSEY trials showed that alirocumab as an add-on statin therapy achieved significantly greater reduction in the LDL-C level than placebo (Bays et al., 2015; Cannon et al., 2015; Kastelein et al., 2015; Kereiakes et al., 2015; Robinson et al., 2015; Farnier et al., 2016; Ginsberg et al., 2016; Roth et al., 2016; Teramoto et al., 2016), ranging from 32 to 70 percent. Similarly, evolocumab as an add-on therapy attained around 46 to 72 percent greater reduction in the LDL-C level than placebo (Giugliano et al., 2012; Raal et al., 2012; Blom et al., 2014; Hirayama et al., 2014; Robinson et al., 2014; Raal et al., 2015a; Raal et al., 2015b; Kiyosue et al., 2016; Sabatine et al., 2017). In 2017, Schmidt et al. conducted a Cochrane systematic review and meta-analysis to evaluate the effect of PCSK9 inhibitors in reducing LDL-C and CVD risk, concluding that PCSK9 inhibitors reduced LDL-C and decreased CVD risk but may have increased the risk of any adverse events and led to little or no difference in mortality (Schmidt et al., 2017).

Inclisiran, a novel therapeutic agent, decreases PCSK9 hepatic synthesis by small interfering RNA (siRNA) (Kosmas et al., 2018). Inclisiran has been recently approved by the European Union since December 2020 for combination use with other lipid-lowering treatments or monotherapy to attain the lipid-lowering goal. ORION trials demonstrated that compared with placebo, inclisiran as an add-on statin therapy effectively reduced around 50% LDL-C level with no severe adverse reaction reported (Ray et al., 2017; Ray et al., 2020).

However, limited head-to-head studies compare the efficacy and safety of PCSK9 inhibitors to each other as add-on statin therapy. Most recent systematic reviews with meta-analyses have pooled PCSK9 inhibitors as a class (Li et al., 2015; Navarese et al., 2015; Zhang et al., 2015; Lipinski et al., 2016; Peng et al., 2016). Therefore, we conducted a systematic review and network meta-analysis to compare the efficacy of different PCSK9 inhibitors with different dosage as an add-on statin therapy in reducing the levels of LDL-C and lipoproteins e.g., ApoB and Lp(a), which are also important causal agents of atherosclerosis, and reducing cardiac events and the safety in adults with hyperlipidemia.

## METHODS

### Search Strategy and Selection Criteria

Two investigators (Y-T Huang and L-T Ho) independently searched PubMed, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov, by applying the following keywords: "HMG-CoA reductase inhibitor*" or "Statin*" and "Proprotein convertase subtilisin*kexin type 9" or "Alirocumab" or "REGN727" or "SAR236553" 'Praluent" or "Evolocumab" or "AMG 145" or "Repatha" or "Bococizumab" or "RN316" or "PF-04950615" or "Frovocimab" or "LY3015014" or "Inclisiran" or "ALN-PCSsc" or "RG7652" or "MPSK-3169A" or "Ebronucimab" or "AK102" or "JS002" or "Lerodalcibep" or "IBI306" or "CIVI007" from inception to April 20, 2021, without language restrictions. Detailed search strategies and the study protocol are provided in **Supplementary Appendix S1**. The study protocol was registered in the International Prospective Register of Systematic Reviews (CRD42017067529).

Studies to be included in our systematic review needed to fulfill the following criteria: 1) patients were randomly allocated to different treatments; 2) patients had one of the following conditions: LDL-C greater than 70 mg/dl, hypercholesterolemia, hyperlipidemia, mixed dyslipidemia, or high cardiovascular risk; 3) the study included comparisons of PCSK9 inhibitor therapies, with ezetimibe or placebo control; 4) the therapies should be add-on statin therapy; 5) the study reported changes in LDL-C, ApoB, or Lp(a); 6) the study was a phase 3 clinical trial. We excluded the bococizumab-related trials because the drug was discontinued for further development and was not approved for medical use.

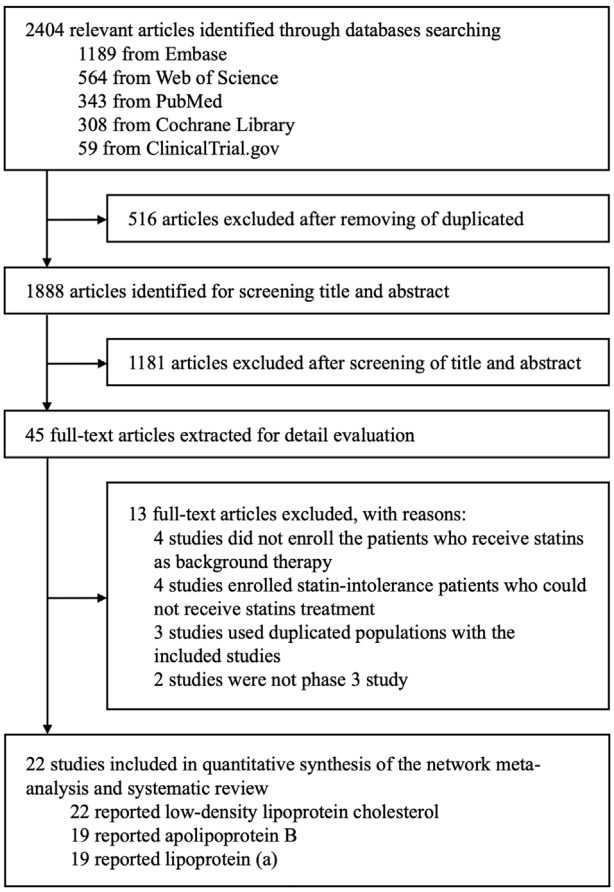


**FIGURE 1 |** Flow chart of study identification and eligibility.

## Data Extraction and Quality Assessment

Two investigators (Y-T Huang and L-T Ho) independently reviewed full manuscripts of eligible studies. We used a structured database to ensure accuracy of data extraction (**Figure 1**). For a dose-ranging study, we included the doses: Alirocumab 75 mg or 150 mg biweekly (Q2W) and 300 mg monthly (QM); evolocumab 140 mg biweekly (Q2W) and 420 mg monthly (QM); inclisiran 300 mg with initial 3-month interval and every 6 months into the network meta-analysis. For efficacy analysis, the percentage changes in LDL-C, ApoB, and Lp(a) and the associated standard errors were extracted. For safety evaluation, the numbers of patients with the occurrence of adverse events (AEs), such as nasopharyngitis, injection-site reaction, or serious adverse events (SAEs), during the period from the initial injection to the end of study drug effect were extracted. When data required for our review were incomplete or lacked sufficient details, we contacted the original authors to request further information by email.

The same investigators independently assessed the study quality to evaluate the potential biases within the included studies. The studies were given a score of low, unclear, or high risk for selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias following the Cochrane Review Group's Study Quality Guide, and the result of our evaluation was recorded using Review Manager software from the Cochrane Collaboration (Higgins and Green, 2011).

## Statistical Analysis

We conducted a network meta-analysis to compare the efficacy and safety among the PCSK9 inhibitors. The weighted mean differences in LDL-C, ApoB, and Lp(a) with the corresponding 95% CI were estimated for the efficacy of different PCSK9 inhibitors relative to placebo or ezetimibe. The odds ratio (OR) with the corresponding 95% CI was estimated for the incidence of AEs. In a frequentist setting, random-effects network meta-analysis combined direct and indirect evidence to provide a comprehensive evaluation of PCSK9 inhibitors. Within the network meta-analysis, we evaluated the consistency of evidence using three methods: 1) The design-by-treatment interaction model to evaluate the consistency in treatment effects between studies with different sets of treatments; 2) the loop inconsistency model to evaluate consistency in evidence with a closed loop; and 3) the node-splitting model to examine the difference between direct and indirect evidence for each pair of treatment (Salanti et al., 2008; Higgins et al., 2012; Tu, 2015; Yu-Kang, 2016). Moreover, we calculated the ranking probabilities for each treatment by undertaking 1,000 simulations to calculate the percentage of simulations for the performance of a treatment relative to other treatments in the network (Salanti et al., 2011). Heterogeneity was assessed using the Cochran Q test and the $I^2$ statistic. $I^2$ values of 25, 50, and 75% represented mild, moderate, and severe heterogeneity, respectively (Higgins et al., 2003). Small study or publication bias was examined by the funnel plot, Egger's regression test, and Begg's rank test (Egger et al., 1997). Sensitivity analyses were carried out to test the robustness of the study results. Statistical significance set at $p < 0.05$ was used for all statistical analyses. All analyses were conducted using R statistical software, version 3.6.1, with the package "netmeta". Our analyses were in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension (Page et al., 2021).

# RESULTS

A total of 2,404 articles were identified through database searching, and 1,888 articles remained after removing duplicates by screening the titles and abstracts. Among them, 1,843 articles that did not fulfill the inclusion criteria were excluded. The full texts of 45 potential articles were obtained for further assessment. Eventually, 22 articles with 42,786 patients were included in this systemic review and network meta-analysis (**Figure 1**).

## Basic Characteristics of Included Trials

Among 22 articles, 12 were alirocumab-based studies with 6,692 patients, eight were evolocumab-based studies with 32,434

**TABLE 1 |** Characteristics of included studies.

| No | Year | Author | Trial | Duration, week(s) | Study population | Add-on therapy | Dosage of PCSK9 inhibitor (mg) | Sample size | Age, mean (SD) | Women, % | HP, % | DM, % | LDL-C, mean (SD) | ApoB, mean (SD) | Lp(a), median (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alirocumab | | | | | | | | | | | | | | | |
| 1 | 2015 | Bays H | ODYSSEY OPTIONS I | 12/24 | LDL-C ≥ 70 mg/dl with CVD or LDL-C ≥ 100 mg/dl with CVD risk factors | Alirocumab | 75 | 57 | 62.2 (10.0) | 42.1 | 77.2 | 57.9 | 103.9 (34.9) | 90.0 (21.9) | 24.0 (52.6) |
| | | | | | | Ezetimibe | 0 | 55 | 65.7 (9.0) | 43.6 | 81.8 | 52.7 | 100.4 (29.5) | 89.2 (22.6) | 21.0 (27.4) |
| | | | | | | Alirocumab | 75 | 47 | 64.2 (10.4) | 34 | 76.6 | 53.2 | 116.4 (37.4) | 97.0 (25.5) | 21.0 (44.4) |
| | | | | | | Ezetimibe | 0 | 47 | 63.9 (10.3) | 23.4 | 78.7 | 34 | 98.9 (29.2) | 83.3 (17.0) | 32.0 (36.3) |
| 2 | 2015/ 2017 | Cannon CP/El Shahawy M | ODYSSEY COMBO II | 24/52 | LDL-C ≥ 70 mg/dl with CVD or LDL-C ≥ 100 mg/dl without CVD | Alirocumab | 75 | 479 | 61.7 (9.4) | 24.8 | — | 30.3 | 108.1 (34.7) | 90.0 (20.0) | 28.0 (44.8) |
| | | | | | | Ezetimibe | 0 | 241 | 61.3 (9.2) | 29.5 | — | 31.5 | 104.2 (34.7) | 90.0 (20.0) | 22.4 (36.4) |
| 3 | 2015 | Kastelein JJP | ODYSSEY FH I, ODYSSEY FH II | 24 | LDL-C ≥ 70 mg/dl and TG ≤ 400 mg/dl with HeFH | Alirocumab | 75 | 323 | 52.1 (12.9) | 44.3 | 43 | 9.9 | 144.7 (52.1) | 114.6 (30.7) | 51.5 (2.8) |
| | | | | | | Placebo | 0 | 163 | 51.7 (12.3) | 42.3 | 43.6 | 15.3 | 144.4 (37.0) | 113.7 (28.4) | 46.9 (4.0) |
| | | | | | | Alirocumab | 75 | 167 | 53.2 (12.9) | 48.5 | 34.1 | 4.2 | 134.6 (37.5) | 108.0 (27.7) | 49.9 (5.4) |
| | | | | | | Placebo | 0 | 82 | 53.2 (12.5) | 45.1 | 29.3 | 3.7 | 134.0 (26.3) | 107.7 (23.9) | 50.9 (6.6) |
| 4 | 2015 | Kereiakes DJ | ODYSSEY COMBO I | 24 | LDL-C ≥ 70 mg/dl with CVD or LDL-C ≥ 100 mg/dl with CHD risk | Alirocumab | 75 | 209 | 63.0 (9.5) | 37.3 | — | 45 | 100.2 (29.5) | 90.8 (21.4) | 31.0 (54.1) |
| | | | | | | Placebo | 0 | 107 | 63.0 (8.8) | 28 | — | 39.3 | 106.0 (35.3) | 91.4 (24.1) | 38.0 (44.4) |
| 5 | 2015 | Robinson JG | ODYSSEY LONG TERM | 24 | LDL-C ≥ 70 mg/dl with HeFH or CHD | Alirocumab | 150 | 1,530 | 60.4 (10.4) | 36.7 | — | 34.9 | 122.7 (42.6) | 101.9 (27.7) | 22.2 (43.6) |
| | | | | | | Placebo | 0 | 780 | 60.6 (10.4) | 39.8 | — | 33.9 | 121.9 (41.4) | 101.1 (27.3) | 20.9 (44.7) |
| 6 | 2016 | Farnier M | ODYSSEY OPTIONS II | 12/24 | LDL-C ≥ 70 mg/dl with CVD or LDL-C ≥ 100 mg/dl with CVD risk factors | Alirocumab | 75 | 49 | 62.2 (11.1) | 36.7 | 73.5 | 38.8 | 106.0 (29.1) | 93.4 (22.6) | 22.0 (48.9) |
| | | | | | | Ezetimibe | 0 | 48 | 60.4 (10.4) | 45.8 | 68.8 | 47.9 | 94.7 (33.6) | 89.0 (25.9) | 38.5 (68.1) |
| | | | | | | Alirocumab | 75 | 54 | 57.9 (8.9) | 48.1 | 74.1 | 33.3 | 114.1 (30.0) | 92.7 (25.2) | 49.5 (65.9) |
| | | | | | | Ezetimibe | 0 | 53 | 63.1 (10.2) | 41.5 | 67.9 | 39.6 | 115.2 (48.4) | 97.8 (20.4) | 35.5 (45.2) |
| 7 | 2016 | Ginsberg HN | ODYSSEY HIGH FH | 24 | LDL-C ≥ 160 mg/dl with HeFH | Alirocumab | 150 | 72 | 49.8 (14.2) | 51.4 | 55.6 | 12.5 | 196.3 (57.9) | 138.2 (32.0) | 22.0 (31.1) |
| | | | | | | Placebo | 0 | 35 | 52.1 (11.2) | 37.1 | 60 | 17.1 | 201.0 (43.4) | 146.6 (28.3) | 30.0 (23.0) |
| 8 | 2016 | Roth EM | ODYSSEY CHOICE I | 24 | LDL-C ≥70 mg/dl with moderate-to-very-high CVD risk or LDL-C ≥ 100 mg/d with moderate CVD risk | Alirocumab | 75 | 78 | 60.7 (9.1) | 34.6 | — | 28.2 | 118.0 (35.1) | 99.6 (25.0) | 28.0 (35.9) |
| | | | | | | Alirocumab | 300 | 312 | 61.6 (10.0) | 39.1 | — | 30.8 | 115.4 (30.6) | 96.6 (21.3) | 27.0 (43.0) |
| | | | | | | Placebo | 0 | 157 | 61.6 (9.7) | 35.7 | — | 31.8 | 115.8 (37.2) | 96.0 (24.3) | 25.5 (48.9) |
| 9 | 2016 | Teramoto T | ODYSSEY JAPAN | 24 | LDL-C ≥100 mg/dl with HeFH or Non-FH with high CAD risk or LDL-C ≥ 120 mg/dl | Alirocumab | 75 | 144 | 60.3 (9.7) | 41.7 | — | 72.9 | 142.9 (27.0) | 110.0 (20.0) | 16.8 (19.1) |
| | | | | | | Placebo | 0 | 72 | 61.8 (9.0) | 34.7 | — | 59.7 | 142.9 (27.0) | 110.0 (20.0) | 14.7 (18.7) |
| 10 | 2017 | Leiter LA | ODYSSEY DM-INSULIN | 24 | LDL-C levels ≥70 mg/dl | Alirocumab | 75 | 294 | 63.9 (8.9) | 45.2 | — | 100 | 112.1 (34.3) | 97.0 (24.7) | 16.0 (37.0) |
| | | | | | | Placebo | 0 | 147 | 64.0 (9.4) | 46.9 | — | 100 | 110.5 (37.4) | 96.2 (26.8) | 14.0 (24.4) |
| | | | | | | Alirocumab | 75 | 51 | 54.9 (10.1) | 43.1 | — | 100 | 127.7 (58.1) | 99.7 (35.6) | 17.0 (16.3) |
| | | | | | | Placebo | 0 | 25 | 58.5 (7.8) | 32 | — | 100 | 109.8 (31.4) | 87.0 (21.0) | 12.0 (24.4) |
| 11 | 2018 | Koh KK | ODYSSEY KT | 24 | LDL-C ≥ 70 mg/dl with a history of documented CVD, or LDL-C ≥ 100 mg/dl without such history | Placebo | 0 | 102 | 60.1 (9.1) | 20.6 | — | 37.3 | 99.3 (25.2) | 85.6 (17.7) | 24.5 (33.3) |
| | | | | | | Alirocumab | 75 | 97 | 61.2 (10.4) | 14.4 | — | 33 | 97.0 (27.8) | 81.7 (17.2) | 23.0 (31.1) |
| 12 | 2019 | Han Y | ODYSSEY EAST | 24 | LDL-C ≥ 70 mg/dl with CVD or LDL-C ≥ 100 mg/dl without CVD | Alirocumab | 75 | 407 | 58.8 (10.7) | 22.6 | 63.4 | 29.7 | 110.7 (48.5) | 94.7 (28.6) | 28.0 (47.0) |
| | | | | | | Ezetimibe | 0 | 208 | 58.3 (11.2) | 29.8 | 53.4 | 23.1 | 111.2 (49.8) | 95.5 (30.5) | 31.0 (50.0) |

(Continued on following page)

**TABLE 1 |** (*Continued*) Characteristics of included studies.

| No | Year | Author | Trial | Duration, week(s) | Study population | Add-on therapy | Dosage of PCSK9 inhibitor (mg) | Sample size | Age, mean (SD) | Women, % | HP, % | DM, % | LDL-C, mean (SD) | ApoB, mean (SD) | Lp(a), median (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Evolocumab | | | | | | | | | | | | | | | |
| 13 | 2014 | Blom DJ | DESCARTES | 52 | LDL-C ≥ 75 mg/dl and TG ≤ 400 mg/dl | Placebo | 0 | 129 | 57.0 (10.6) | 21.3 | 39.5 | 7.8 | 98.4 (14.5) | 82.6 (11.0) | 12.1 (28.7) |
| | | | | | | Evolocumab | 420 | 254 | 57.2 (10.3) | 57.1 | 42.9 | 6.7 | 101.3 (15.1) | 84.0 (12.6) | 12.1 (21.3) |
| | | | | | | Placebo | 0 | 73 | 58.4 (8.7) | 54.8 | 56.2 | 19.2 | 96.2 (13.3) | 83.3 (12.4) | 21.7 (49.1) |
| | | | | | | Evolocumab | 420 | 145 | 57.8 (9.4) | 47.6 | 57.9 | 13.1 | 94.6 (12.9) | 83.3 (12.5) | 30.8 (52.8) |
| | | | | | | Placebo | 0 | 63 | 55.9 (9.0) | 47.6 | 60.3 | 25.4 | 119.8 (32.4) | 100.3 (22.1) | 26.3 (65.4) |
| | | | | | | Evolocumab | 420 | 126 | 54.2 (11.5) | 44.4 | 54 | 19.8 | 116.8 (35.3) | 95.5 (23.6) | 27.9 (48.2) |
| 14 | 2014 | Robinson JG | LAPLACE-2 | 12 | LDL-C ≥ 80 mg/dl with intensive statin and TG ≤ 400 mg/dl | Placebo | 0 | 56 | 58.3 (10.5) | 42.9 | — | 16.1 | 123.0 (46.6) | 95.3 (26.0) | 13.1 (23.0) |
| | | | | | | Placebo | 0 | 55 | 62.2 (10.4) | 50.9 | — | 12.7 | 123.7 (47.9) | 95.3 (29.6) | 17.1 (28.1) |
| | | | | | | Ezetimibe | 0 | 56 | 61.0 (9.0) | 51.8 | — | 10.7 | 126.8 (49.6) | 101.3 (31.2) | 15.4 (55.7) |
| | | | | | | Ezetimibe | 0 | 55 | 60.6 (9.2) | 50.9 | — | 20 | 119.3 (28.1) | 94.6 (20.4) | 13.8 (47.8) |
| | | | | | | Evolocumab | 140 | 110 | 58.3 (8.4) | 50.9 | — | 20.9 | 124.2 (43.4) | 99.7 (26.4) | 11.3 (34.6) |
| | | | | | | Evolocumab | 420 | 110 | 59.6 (11.1) | 40 | — | 13.6 | 126.1 (50.4) | 97.3 (28.9) | 20.4 (48.8) |
| | | | | | | Placebo | 0 | 55 | 57.1 (9.9) | 40 | — | 12.7 | 100.3 (36.2) | 81.1 (22.1) | 24.6 (50.0) |
| | | | | | | Placebo | 0 | 55 | 58.8 (11.5) | 43.6 | — | 18.2 | 94.7 (31.9) | 80.1 (21.4) | 20.8 (42.9) |
| | | | | | | Ezetimibe | 0 | 56 | 60.5 (10.2) | 42.9 | — | 17.9 | 98.7 (34.0) | 85.3 (23.1) | 10.4 (29.6) |
| | | | | | | Ezetimibe | 0 | 54 | 61.1 (8.9) | 51.9 | — | 31.5 | 92.3 (19.3) | 78.7 (16.7) | 25.6 (55.5) |
| | | | | | | Evolocumab | 140 | 109 | 59.7 (10.2) | 39.4 | — | 14.7 | 94.2 (34.8) | 79.9 (25.1) | 13.3 (38.3) |
| | | | | | | Evolocumab | 420 | 110 | 60.1 (10.2) | 43.6 | — | 16.4 | 93.8 (32.3) | 77.9 (21.5) | 10.2 (26.3) |
| | | | | | | Placebo | 0 | 56 | 61.9 (9.7) | 57.1 | — | 17.9 | 110.3 (28.0) | 91.6 (18.4) | 14.2 (46.3) |
| | | | | | | Placebo | 0 | 55 | 61.5 (10.3) | 50.9 | — | 20 | 108.6 (30.9) | 89.8 (20.7) | 14.6 (44.0) |
| | | | | | | Evolocumab | 140 | 112 | 59.7 (9.2) | 40.2 | — | 17.9 | 114.9 (34.9) | 94.2 (24.0) | 15.8 (47.5) |
| | | | | | | Evolocumab | 420 | 115 | 61.5 (9.6) | 51.3 | — | 13 | 123.7 (48.5) | 96.5 (27.5) | 13.3 (50.3) |
| | | | | | | Placebo | 0 | 58 | 61.2 (9.1) | 60.3 | — | 5.2 | 115.6 (39.8) | 93.1 (27.3) | 14.2 (46.3) |
| | | | | | | Placebo | 0 | 57 | 59.6 (9.2) | 47.4 | — | 15.8 | 119.9 (39.1) | 95.9 (25.2) | 14.6 (44.0) |
| | | | | | | Evolocumab | 140 | 113 | 58.9 (11.2) | 45.1 | — | 23 | 118.7 (40.9) | 95.4 (27.0) | 15.8 (47.5) |
| | | | | | | Evolocumab | 420 | 115 | 59.3 (10.5) | 44.3 | — | 10.4 | 122.9 (42.0) | 97.2 (26.9) | 13.3 (50.3) |
| | | | | | | Placebo | 0 | 56 | 60.2 (8.7) | 37.5 | — | 3.6 | 77.4 (20.9) | 71.0 (16.6) | 11.9 (50.6) |
| | | | | | | Placebo | 0 | 55 | 58.1 (11.4) | 47.3 | — | 10.9 | 102.9 (49.3) | 84.8 (29.7) | 13.8 (42.3) |
| | | | | | | Evolocumab | 140 | 111 | 59.5 (9.2) | 38.7 | — | 16.2 | 88.5 (31.5) | 77.4 (22.3) | 17.1 (53.4) |
| | | | | | | Evolocumab | 420 | 112 | 59.6 (9.0) | 46.4 | — | 10.7 | 88.5 (31.3) | 78.7 (23.1) | 20.6 (53.5) |
| 15 | 2015 | Raal FJ | TESLA Part B | 12 | HoFH | Placebo | 0 | 16 | 32 (14) | 50 | — | — | 335.9 (146.7) | 210.0 (80.0) | 53.3 (37.3) |
| | | | | | | Evolocumab | 420 | 33 | 30 (12) | 48 | — | — | 355.2 (135.1) | 210.0 (70.0) | 31.7 (36.7) |
| 16 | 2015 | Raal FJ | RUTHERFORD-2 | 12 | HeFH | Placebo | 0 | 54 | 51.1 (14.2) | 46 | — | — | 150.6 (34.7) | 110.0 (30.0) | 18.3 (25.0) |
| | | | | | | Evolocumab | 140 | 110 | 52.6 (12.3) | 40 | — | — | 154.4 (50.2) | 120.0 (30.0) | 32.3 (54.5) |
| | | | | | | Placebo | 0 | 55 | 46.8 (12.1) | 44 | -— | — | 150.6 (42.5) | 110.0 (20.0) | 36.3 (56.5) |
| | | | | | | Evolocumab | 420 | 110 | 51.9 (12.0) | 42 | — | — | 154.4 (42.5) | 110.0 (30.0) | 25.4 (54.6) |
| 17 | 2016 | Kiyosue A | YUKAWA-2 | 12 | LDL-C ≥ 100 mg/dl and TG ≤ 400 mg/dl | Placebo | 0 | 202 | 61.0 (10.0) | 39 | 72 | 51 | 103.0 (28.0) | 92.0 (20.0) | 12.9 (11.7) |
| | | | | | | Evolocumab | 140/420 | 202 | 62.0 (11.0) | 40 | 75 | 47 | 109.0 (35.0) | 96.0 (25.0) | 14.2 (14.5) |
| 18 | 2017 | Sabatine MS | FOURIER | 12 | LDL-C ≥ 70 mg/dl with atherosclerotic vascular disease or LDL-C ≥ 100 mg/dl without atherosclerotic vascular disease | Evolocumab | 140/420 | 13,784 | 32.5 (9.1) | 24.6 | 80.1 | 36.7 | 92 (21.5) | — | 15.4 (47.2) |
| | | | | | | Placebo | 0 | 13,780 | 62.5 (8.9) | 24.5 | 80.1 | 36.5 | 92 (21.5) | — | 15.4 (46.6) |

(Continued on following page)

**TABLE 1 |** (*Continued*) Characteristics of included studies.

| No | Year | Author | Trial | Duration, week(s) | Study population | Add-on therapy | Dosage of PCSK9 inhibitor (mg) | Sample size | Age, mean (SD) | Women, % | HP, % | DM, % | LDL-C, mean (SD) | ApoB, mean (SD) | Lp(a), median (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2019 | Lorenzatti AJ | BERSON | 12 | LDL-C ≥100 mg/dl with DM | Evolocumab | 140/420 | 657 | 62 (34.8) | 55.9 | 72.8 | 100 | 92.8 (34.8) | — | 28.9 (39.3) |
| | | | | | | Placebo | 0 | 324 | 62 (33.3) | 60.2 | 73.8 | 100 | 92.8 (30.9) | — | 28.9 (39.0) |
| 19 | 2019 | Rosenson RS | BANTING | 12 | LDL-C ≥70 mg/dl and non-HDL-C ≥100 mg/dl with DM and CVD, or LDL-C ≥100 mg/dl and non-HDL-C ≥130 mg/dl with DM and without CVD | Evolocumab | 420 | 280 | 62.5 (8.5) | 42.9 | 88.2 | 100 | 108.7 (30.9) | 97.0 (23.0) | 36.7 (46.5) |
| 20 | | | | | | Placebo | 0 | 141 | 62.2 (8.4) | 46.1 | 84.4 | 100 | 110.6 (32.9) | 98.0 (22.0) | 41.4 (51.2) |
| Inclisiran | | | | | | | | | | | | | | | |
| | 2020 | Raal FJ | ORION-9 | 78 | LDL-C ≥100 mg/dL with FH | Inclisiran | 300 | 242 | 56 (11.9) | 53.7 | 42.1 | 8.3 | 151.4 (50.4) | 123.8 (33.2) | 23.8 (65.8) |
| | | | | | | Placebo | 0 | 240 | 56 (13.3) | 52.1 | 42.1 | 11.7 | 154.7 (58.0) | 124.5 (34.8) | 22.5 (68.8) |
| 21 | 2020 | Raal KK | ORION-10 | 78 | LDL-C ≥70 mg/dl with ASCVD | Inclisiran | 300 | 781 | 66.4 (8.9) | 31.5 | 91.4 | 47.5 | 104.5 (39.6) | 94.1 (25.6) | 23.8 (72.1) |
| | | | | | | Placebo | 0 | 780 | 65.7 (8.9) | 29.7 | 89.9 | 42.4 | 104.8 (37.0) | 94.6 (25.1) | 23.3 (70.4) |
| 22 | | | ORION-11 | | LDL-C ≥70 mg/dl with ASCVD factors | Inclisiran | 300 | 810 | 64.8 (8.3) | 28.5 | 79 | 36.5 | 107.2 (41.8) | 97.1 (28.0) | 17.5 (66.7) |
| | | | | | | Placebo | 0 | 807 | 84.8 (8.7) | 28 | 81.9 | 33.7 | 103.7 (36.4) | 95.1 (5.2) | 14.6 (67.9) |

*HP: hypertension; DM: type 2 diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; ApoB: apolipoprotein B; Lp(a): lipoprotein(a).*

patients, and two were inclisiran-based studies with 3,660 patients. The basic characteristics of the included studies are summarized in **Table 1**. Risk of bias was assessed in all included studies with seven domains of the Cochrane risk-of-bias assessment tool, which was at low risk of bias (**Supplementary Figures S1, S2**).

## Efficacy Endpoints

The network meta-analysis contained eight treatments, including PCSK9 inhibitors at different dosage, including alirocumab 75 mg/150 mg Q2W, 300 mg QM, and evolocumab 140 mg every Q2W, 420 mg every QM, and inclisiran 300 mg with an initial 3-month interval and every six months versus either ezetimibe or placebo (**Figure 2**).

## Low-Density Lipoprotein Cholesterol

The upper part of **Figure 3** and **Figure 4** present the results of network meta-analyses for LDL-C reduction. Among three PCSK9 inhibitors, evolocumab had greater LDL-C reduction than alirocumab or inclisiran. Evolocumab 140 mg Q2W was ranked as the best among all treatment strategies for lowering LDL-C levels, and the treatment difference was 68.05% (95% CI: 62.43–73.67%) compared with placebo. Evolocumab 140 mg Q2W had greater LDL-C reduction than evolocumab 420 mg QM [58.01% (53.65%, 62.37%)], alirocumab 75/150 mg Q2W [53.72% (49.75%, 57.70%)], and inclisiran 300 mg [47.90% (35.54%, 60.26%)] (**Supplementary Figure S5**). However, evolocumab 420 mg QM had similar LDL-C level reduction effects compared with those of alirocumab 300 mg QM [59.70% (48.01%, 71.38%)]. Compared with ezetimibe, all PCSK9 inhibitors had significant effects on LDL-C reduction. Nevertheless, as an add-on lipid-lowering therapy, ezetimibe still significantly reduced LDL-C levels compared with placebo.

## Apolipoprotein B

The middle part of **Figure 3** presents the results of network meta-analyses for ApoB reduction. Among three PCSK9 inhibitors, all significantly reduced ApoB levels compared with placebo. As the trend of LDL-C reduction, evolocumab had greater ApoB reduction than alirocumab. Evolocumab 140 mg Q2W was ranked the best among all treatment strategies (inclisiran was excluded because no ApoB lowering data were available for lowering ApoB levels, and the treatment difference was 54.95% [49.55% and 60.35%) compared with placebo, but similar compared with alirocumab 300 mg QM [49.41% (38.22%, 60.60%)] (**Supplementary Figure S5**).

Evolocumab 140 mg Q2W had greater ApoB reduction than evolocumab 420 mg QM [46.22% (46.06%, 50.37%)] and alirocumab 75/150 mg Q2W [42.42% (38.54%, 46.29%)]. Compared with ezetimibe, different dosages of evolocumab and alirocumab had significant effects on ApoB reduction. Nevertheless, as an add-on lipid-lowering therapy, ezetimibe still significantly reduced LDL-C levels compared with placebo.

## Lipoprotein (a)

The lower part of **Figure 3** presents the results of network meta-analyses for Lp(a) reduction. Among three PCSK9 inhibitors, all

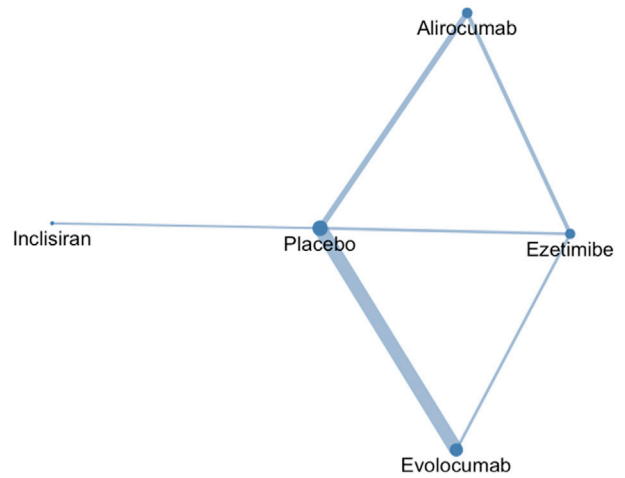


**FIGURE 2 |** Network geometry of low-density lipoprotein cholesterol. The sizes of treatment nodes reflect the number of patients randomly assigned to each treatment. The thicknesses of edges represent the number of studies underlying each comparison.

significantly reduced Lp(a) levels compared with placebo. However, the effects of each PCSK-9 on Lp(a) were different from the effects on LDL-C or ApoB, although evolocumab 140 mg Q2W remained the best ranking among all treatment strategies for lowering Lp(a) levels [34.25% (27.59%, 40.91%)] compared with placebo. However, the differences in Lp(a) reduction were not significantly different between evolocumab and alirocumab at different dosages.

## Safety Endpoints

Regarding the safety of PCSK9 inhibitors, no significant risk of AEs, SAEs, or nasopharyngitis were noted (Contois et al., 2009). Only inclisiran increased the risk of injection-site reaction. This study suggests that PCSK9 inhibitors were safe with tolerable side effects as an adjuvant lipid-lowering therapy.

## Bias Assessment, Inconsistency Assessment, and Sensitivity Analyses

Although Egger's test implied that there might be publication bias for percentage change in ApoB (**Supplementary Figures S19, S20**), the funnel plot showed that the possible source of asymmetry might be from larger studies, which might be resulted from heterogeneity. For the assessment of publication bias for AEs from PCSK9 inhibitors, no significant publication bias was found. For the inconsistency assessment (**Supplementary Table S1**), overall inconsistency between the designs-interaction random-effect model was not found. Sensitivity analyses were performed using an alternative meta-analysis model, that is, the fixed-effect model, and the results remained consistent with our main results (**Supplementary Figures S26, S27**).

# DISCUSSION

The present study evaluated the efficacy and safety of different PCSK9 inhibitors as adjuvant therapies in statin-treated hypercholesterolemic patients. The statin used in the included trials were maximally tolerated statin therapy; most of the doses the trials applied were moderate-to-high intensity statin dose, that is, atorvastatin 20, 40, or 80 mg once a day; rosuvastatin 20 or 40 mg once a day; and simvastatin 40 mg or 80 mg once a day. Moderate-to-high intensity statin therapy causes 30 to 50% LDL-C reduction (Oesterle et al., 2017). This study revealed that statin add-on PCSK9 inhibitors, including evolocumab, alirocumab, and inclisiran vs. placebo or ezetimibe, significantly reduced the levels of LDL-C, ApoB, and Lp(a). Among the PCSK9 inhibitors, evolocumab 140 mg Q2W was found to be more superior in atherogenic lipid reduction, including LDL-C, ApoB, and Lp(a), than the others except for alirocumab 300 mg QM. PCSK9 inhibitors have similar side effects other than higher injection-site reaction caused by inclisiran. The approving risk-benefit results of evolocumab, alirocumab, and inclisiran in lipid lowering was consistent with previous literature (Strilchuk et al., 2019). However, the results of PCSK9 inhibitor benefit–risk ratio still need to be interpreted cautiously due to the AE of PCSK9 inhibitors being such rare events that the statistical power to detect the difference among studies may be relatively insufficient.

Previous meta-analyses found that compared with non–anti-PCSK9 treatment, anti-PCSK9 treatment noticeably reduced lipid profiles, and the incidence of AEs did not increase. These traditional meta-analyses combined all PCSK9 treatments into a single group of anti-PCSK9 treatments, so it did not provide information about the potential differences in efficacy and safety between various PCSK9 treatments (Li et al., 2015; Navarese et al., 2015; Zhang et al., 2015). Our study found significant differences in treatment efficacy among different PCSK9 inhibitors, and evolocumab appeared to be the best ranking PCSK9 inhibitor in reducing atherogenic lipid level, including LDL-C, ApoB, and Lp(a). In 2017, Toth et al. conducted a systematic review and meta-analysis, revealing that PCSK9 inhibitors as an add-on therapy significantly reduce LDL-C and demonstrating that evolocumab vs. alirocumab had larger reduction in the LDL-C level, which are consistent with our study results (Toth et al., 2017). However, the current study further included the trials of inclisiran to compare the lipid-lowering ability among the previous two PCSK9 inhibitors and the novel PCSK9-inhibiting agent.

The probable biological mechanism to explain our study results was that PCSK9 inhibitor vs. statin provides a further LDL-C level lowering by interfering in PCSK9 function. Evolocumab and alirocumab are human monoclonal antibodies that target PCSK9 approved for LDL-C reduction (Everett et al., 2015; Macchi et al., 2021). Inclisiran, a novel therapeutic agent, decreases PCSK9 hepatic synthesis by small interfering RNA (siRNA) (Ray et al., 2017; Kosmas et al.,

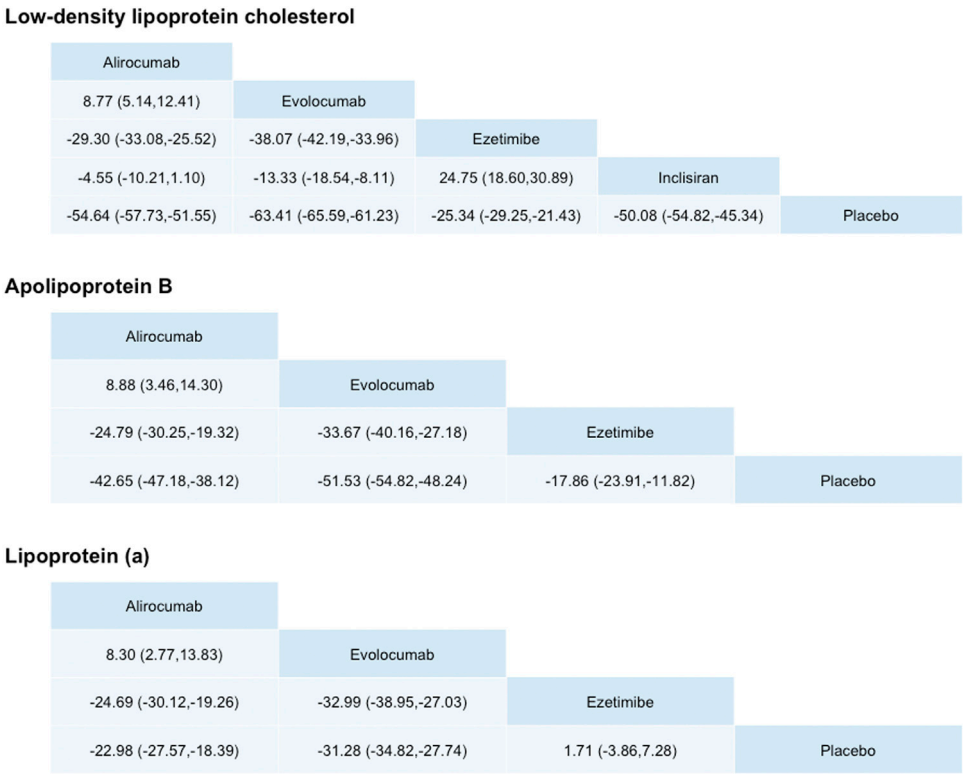


**FIGURE 3 |** Differences in percentage changes in low-density lipoprotein cholesterol, ApoB, and lipoprotein (a) obtained by network meta-analysis. Comparisons should be read from left to right. A positive value favors the column treatment.

2018). The monoclonal antibodies inhibiting PCSK9 function and small interfering RNA reducing PCSK9 synthesis led to higher hepatic LDL-R expression and lower plasma LDL-C levels. The LDL-C level has long been the primary target for cardiovascular risk prevention; thus, further LDL-C lowering may be beneficial for the further reduction of cardiovascular risk. Besides LDL-C lowering, substantial ApoB and Lp(a) lowering caused by PCSK9 inhibitors in statin-treated hypercholesteremia patients may contribute to additional reduction of residual cardiovascular risk (Sacks, 2006; Ridker et al., 2008; Lieb et al., 2018). The discrepancy of the degree of LDL-C and ApoB reduction may be due to the different physiologic roles in lipid metabolism. LDL-C represents the cholesterol mass of LDL particles, while ApoB reflects the total number of LDL, VLDL, and other atherogenic lipoprotein particles due to each of these lipoproteins being with one ApoB molecule. PCSK9 inhibitors keep LDL receptors from degradation to increase LDL-C uptake into cells for metabolism. However, not only LDL particles but also other atherogenic lipoproteins include ApoB, thus resulting in the dissociation between LDL-C and ApoB reduction trend (Sacks, 2006).

The latest 2017 update of ESC/EAS Task Force on practical clinical guidance for PCSK9 inhibitors (Landmesser et al., 2018) suggested that in atherosclerotic cardiovascular disease (ASCVD) patients with substantially elevated LDL-C levels, a PCSK9 inhibitor should be considered despite maximally tolerated statin with or without ezetimibe therapy or inability to tolerate appropriate doses of at least three statins, especially if there are additional indications of increased cardiovascular risk. Our study results provided robust evidence about the potent atherogenic lipid-lowering ability and safety of the PCSK9 inhibitors as adjuvant lipid-lowering treatments. In addition, this study revealed that evolocumab had greater lipid reduction than alirocumab or inclisiran. Moreover, evolocumab Q2W may be the best ranking choice in lipid lowering among all PCSK9 inhibitors at different dosages. However, mentioned knowledge gaps in the clinical guideline were noted concerning the application of the PCSK9 inhibitors, including interindividual variability, long-term efficacy, and especially long-term safety, thus further longitudinal studies are still warranted (Landmesser et al., 2018; Nelson et al., 2019; Kosmas et al., 2020).

Some limitations in the present study must be noted. First, we included PCSK9 inhibitors as adjunctive therapies studies with incomplete information about the background statin therapy. The impact of different statin dosages on the reduction in lipids was neglected in the present study. Second, since PCSK9 inhibitors are novel agents, evidence from randomized control trials is just emerging. For instance, our literature search only found two articles on inclisiran, and therefore, the confidence intervals of estimates on the efficacy and safety were relatively unstable, especially for the indirect estimation. Third, since the

**Adverse event**

| | | | | |
|---|---|---|---|---|
| Alirocumab | | | | |
| 1.05 (0.88,1.26) | Evolocumab | | | |
| 1.12 (0.94,1.34) | 1.07 (0.86,1.33) | Ezetimibe | | |
| 0.97 (0.79,1.20) | 0.93 (0.76,1.13) | 0.87 (0.67,1.12) | Inclisiran | |
| 1.01 (0.88,1.17) | 0.96 (0.85,1.09) | 0.90 (0.73,1.10) | 1.04 (0.89,1.22) | Placebo |

**Severe adverse event**

| | | | | |
|---|---|---|---|---|
| Alirocumab | | | | |
| 0.84 (0.56,1.26) | Evolocumab | | | |
| 0.98 (0.73,1.32) | 1.17 (0.72,1.90) | Ezetimibe | | |
| 1.12 (0.89,1.42) | 1.33 (0.89,1.99) | 1.14 (0.79,1.65) | Inclisiran | |
| 0.96 (0.81,1.14) | 1.14 (0.79,1.65) | 0.98 (0.70,1.37) | 0.86 (0.73,1.01) | Placebo |

**Nasopharyngitis**

| | | | | |
|---|---|---|---|---|
| Alirocumab | | | | |
| 1.07 (0.74,1.54) | Evolocumab | | | |
| 1.04 (0.56,1.96) | 0.97 (0.47,2.02) | Ezetimibe | | |
| 0.99 (0.71,1.39) | 0.93 (0.61,1.40) | 0.95 (0.47,1.94) | Inclisiran | |
| 1.07 (0.88,1.31) | 1.00 (0.74,1.36) | 1.03 (0.53,1.99) | 1.08 (0.82,1.42) | Placebo |

**Injection-site reaction**

| | | | | |
|---|---|---|---|---|
| Alirocumab | | | | |
| 1.02 (0.73,1.42) | Evolocumab | | | |
| 2.41 (1.03,5.65) | 2.36 (0.95,5.91) | Ezetimibe | | |
| 0.25 (0.12,0.51) | 0.25 (0.13,0.48) | 0.10 (0.03,0.32) | Inclisiran | |
| 1.36 (1.02,1.81) | 1.33 (1.13,1.58) | 0.56 (0.23,1.39) | 5.42 (2.84,10.35) | Placebo |

**FIGURE 4 |** Odds ratios of adverse events, nasopharyngitis, injection-site reaction, and serious adverse events obtained by network meta-analysis. Comparisons should be read from left to right. An odds ratio smaller than 1 favors the column treatment.

presence of publication bias was detected in some scenarios, the trim-and-fill method should be applied to assess how the summary estimate changes when these potentially missing studies are taken into account. However, to the best of our knowledge, the trim-and-fill method has still not been developed for conducting the network meta-analysis, whereas it could only adapt to the traditional meta-analysis. Finally, the R package we used cannot deal with trials with more than two treatments to perform the meta-regression for exploring an effect modifier. Further development of the package in R statistical software for meta-regression in network meta-analysis may be warranted.

## CONCLUSION

In this systematic review and network meta-analysis, PCSK9 inhibitors, as adjuvant treatment in statin-treated hypercholesterolemia patients, were associated with greater reduction in atherogenic lipid level, including LDL-C, ApoB, and Lp(a). Among PCSK9 inhibitors, evolocumab 140 mg Q2W showed significantly larger degrees of LDL-C, ApoB, and Lp(a) reduction than alirocumab 300 mg QM. No significant risk difference of AEs was found between PCSK9 inhibitors and placebo, except the higher injection-site reaction noted in inclisiran use.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

## AUTHOR CONTRIBUTIONS

K-LC, Y-KT, and Y-TH designed the study. Y-TH and L-TH had full access to all the data in the study and tool responsibility for the integrity of the data. Y-TH performed the statistical analyses. Y-TH, L-TH, H-YH, K-LC, and Y-KT revised the manuscript. K-LC and Y-KT contributed equally as corresponding authors to this work.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.832614/full#supplementary-material

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