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Network Meta-Analysis to Compare the Efficacy between Different Classes of PCSK9 Inhibitors, siRNA vs. PCSK9 mAb, in Asian Patients with Hypercholesterolemia at Increased Cardiovascular Risk

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CONCLUSIONS

- This NMA ascertains that in Asian patients with hypercholesterolemia, at increased CV risk taking MTD statins, inclisiran (siRNA) with twice-yearly dosing is expected to achieve clinically meaningful LDL-C reductions comparable to PCSK9i mAbs.

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INTRODUCTION

- Hypercholesterolemia, defined by elevated low-density lipoprotein cholesterol (LDL-C)[1], is associated with atherosclerotic cardiovascular disease (ASCVD), a leading cause of mortality and morbidity[2-5].
- In China prevalence of high LDL-C is on increasing trend, with 8% of adults (≥18 years) with LDL-C >4.1mmol/L in 2018 compared with 5.6% and 7.2% in 2010 and 2015 respectively[6,7].
- The Chinese Guideline on Primary Prevention of Cardiovascular Diseases recommends proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) monoclonal antibodies (mAb) to treat patients with high risk of ASCVD who are unable to tolerate statins, those with initial LDL-C ≥4.9mmol/L and other cardiovascular risk factors[8].
- ORION-18, a recently published phase 3 trial in Asian patients (approximately 75% Chinese) with ASCVD or high risk of ASCVD, established inclisiran's [small interfering RNA (siRNA)] efficacy and safety in this population, with superior LDL-C reduction from baseline through day 330 vs. standard of care[9].

OBJECTIVE

- Network meta-analysis (NMA) was conducted to compare the efficacy of different classes of PCSK9 inhibitors, siRNA vs. PCSK9 mAbs [inclisiran vs. evolocumab, alirocumab, and tafolecimab] in LDL-C reduction, among Asian patients with increased CV risk having elevated LDL-C despite being taking maximally tolerated dose (MTD) statins.

METHODS

Study identification:

- A systematic review was conducted using OvidSP (MEDLINE and Embase), Cochrane (Wiley), Pubmed, and Web of Science databases to identify published randomized controlled trials through January 2023 and supplemented with tafolecimab trial publications (domestic PCSK9i in China). **Figure 1** presents the study selection diagram.

Study selection:

- Evidence from the trials was assessed for feasibility of indirect comparison between PCSK9 mAbs and inclisiran.
- 53 trials identified in the literature search were assessed for feasibility based on the population, comparators, and outcomes of interest.

Study selection:

- Feasibility of performing NMA was determined using the following criteria:
  - Whether there was a connected network comparing the treatments and outcomes of interest.
  - Whether there were differences in study, population, and outcomes characteristics across comparisons that are likely modifiers of the relative treatment effects.
- In the feasibility assessment, 34 studies were excluded based on the following criteria:
  - HeFH or statin intolerant population (n=16).
  - Double statin dose in the placebo arm (n=5).
  - Low or moderate statin dose at baseline (n=4).
  - No outcomes of interest (n=3).
  - Trials including bempedoic acid as treatment (n=4).
  - Research question, timepoint of interest (n=2).
- Bempedoic acid trials were excluded as it is not prescribed in China.
- In this poster, we have presented results of two scenarios where studies including patients with moderate intensity statins were included since in China's clinical practice the majority of clinical prescribing dose is categorized as moderate intensity statins[10].

METHODS (Cont.)

Figure 1. Study selection diagram

Outcomes:

- The primary outcome in our analysis was the percentage (%) change in LDL-C from baseline to week 24 (or closest available timepoint).
- Most of the trials employed mixed effects model repeated measures (MMRM) and reported LDL-C change at week 24; therefore post-hoc analyses of inclisiran ORION trials were conducted applying these methodology to harmonize timepoint of assessment and missing data handling methods across the comparator trials.

Statistical analysis:

- Random effects Bayesian NMA was identified as the most appropriate method of analysis given the number of studies per comparison and observed heterogeneity in trial and patient characteristics.
- Relative treatment effects were estimated as mean differences (MD) and 95% credible intervals (CrI). Results with 95% CrIs that do not overlap zero were considered statistically significant.
- Analyses were conducted for two scenarios including studies with patients on ASCVD and taking moderate intensity statins, with pooled PCSK9i mAbs.
  - **Scenario 1:** pooled evolocumab and alirocumab.
  - **Scenario 2:** pooled evolocumab, alirocumab, and tafolecimab.
- Model convergence and fit, statistical heterogeneity, and inconsistency were assessed.
- Analyses were conducted using R (version 2.40).

RESULTS

- A total of 9 studies were deemed relevant for the relative efficacy assessment between pooled PCSK9i mAbs and inclisiran, including 2 studies each for inclisiran, evolocumab, and alirocumab, and 3 studies for tafolecimab. **Figure 2A** (scenario 1) and **Figure 2B** (scenario 2) represent the network diagrams of the included studies.
- Inclisiran showed superior efficacy over placebo in LDL-C lowering at week 24 (MD: -63.06% [95% CrI: -68.91, -57.34]).

Inclisiran vs. pooled PCSK9i mAbs

- In both the scenarios, inclisiran demonstrated numerically favorable LDL-C change, although the observed benefits were not statistically significant compared to the pooled PCSK9i mAbs [**Table 3A** (scenario 1) and **Table 3B** (scenario 2)].
  - Inclisiran vs. (evolocumab + alirocumab): MD -0.43% (95% CrI: -9.89, 8.82).
  - Inclisiran vs. tafolecimab: MD -3.15% (95% CrI: -12.49, 5.98).
  - Inclisiran vs. (evolocumab + alirocumab + tafolecimab): MD -2.5% (95% CrI: -11.26, 6.22).

Figure 2A. Network diagram scenario 1 (pooled evolocumab and alirocumab)

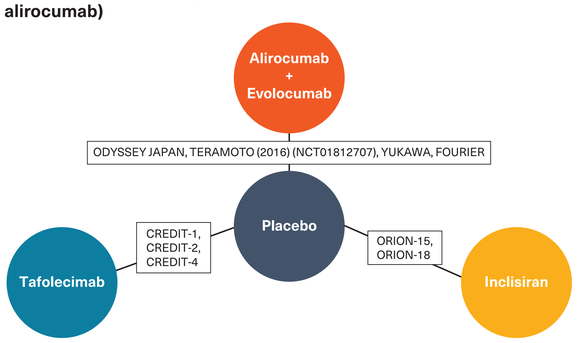
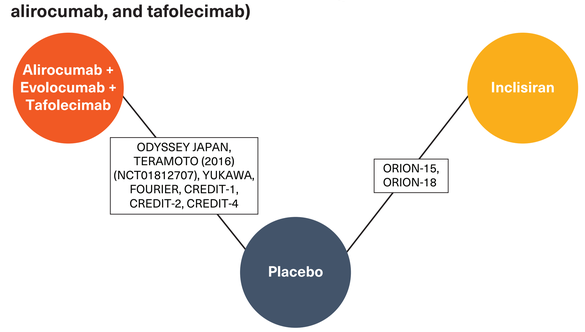


Figure 2B. Network diagram scenario 2 (pooled evolocumab, alirocumab, and tafolecimab)



Abbreviations: Ali, alirocumab; Evo, evolocumab; Inc, inclisiran; Pla, placebo; Tafo, tafolecimab (150mg, 450mg, 600mg)

Table 3A. Relative Treatment Effect Estimates in LDL-C Reduction from Baseline between Inclisiran and Pooled PCSK9i mAbs (Evolocumab and Alirocumab)

Intervention	Relative Treatment Effect Estimation	Placebo	Tafolecimab	Pooled Evolocumab and Alirocumab
Inclisiran	MD (95% CrI)	-63.06 (-69.02, -57.28)	-3.15 (-12.49, 5.98)	-0.43 (-9.89, 8.82)

CrI, credible interval; LDL-C, low density lipoprotein cholesterol; mAbs, monoclonal antibodies; MD, mean difference; PCSK9i, protein convertase subtilisin/kexin type 9 inhibitors

Table 3B. Relative Treatment Effect Estimates in LDL-C Reduction from Baseline between Inclisiran and Pooled PCSK9i mAbs (Evolocumab, Alirocumab, and Tafolecimab)

Intervention	Relative Treatment Effect Estimation	Placebo	Pooled Evolocumab, Alirocumab, and Tafolecimab
Inclisiran	MD (95% CrI)	-63.06 (-68.91, -57.34)	-2.5 (-11.26, 6.22)

CrI, credible interval; LDL-C, low density lipoprotein cholesterol; mAbs, monoclonal antibodies; MD, mean difference; PCSK9i, protein convertase subtilisin/kexin type 9 inhibitors

LIMITATIONS

- Included trials used various definitions for categorizing CV risk and different methods for missing data imputation (e.g., MMRM, last observation carried forward, and pattern mixture models) which results in inconsistency in the analyses. These inconsistencies, coupled with inadequate reporting, precluded meaningful statistical adjustment for their impact.
- In this analysis, data available at week 24 and MMRM as imputation method was preferred but this was not available from all included studies so closest available timepoint to week 24 and subsequent robust imputation method was selected.

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Conflict of interest

Lichang Liu and Abhay Choubey are employees of Novartis.

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