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Comparative Efficacy of Non-Statin Lipid-Lowering Therapies in Patients with Hypercholesterolemia at Increased Cardiovascular Risk: An Updated Network Meta-Analysis

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Introduction

- In 2021, the prevalence of elevated total cholesterol was 59% for England.[1,2] Hypercholesterolemia is associated with atherosclerotic cardiovascular disease (ASCVD), which is a leading cause of mortality worldwide.[3-6] ASCVD affects more than 500 million individuals globally and accounts for 19 million deaths annually.[7]
- Various LDL-C lowering treatments like ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) monoclonal antibodies (mAb), inclisiran (small interfering RNA), and bempedoic acid, have gained approval and are recommended by professional societies, [e.g., European Society of Cardiology (ESC), National Institute of Health and Care Excellence (NICE), American College of Cardiology/American Heart Association (ACC/AHA)] in patients with ASCVD and/or high cardiovascular risk having elevated low-density lipoprotein cholesterol (LDL-C) despite on maximally tolerated statins.[8,9,10]
- A network meta-analysis (NMA) by Burnett et al. 2022[11] compared the efficacy of non-statin lipid lowering therapies (LLTs) inclisiran, PCSK9i mAb (evolocumab, alirocumab), bempedoic acid, and ezetimibe in patients with hypercholesterolemia including ASCVD, heterozygous familial hypercholesterolemia (HeFH), and/or increased CVD risk having elevated LDL-C despite taking maximally-tolerated dose (MTD) statins.
- The objective of our analyses was to update the NMA by Burnett et al. 2022[11] with more recently published trial data and to align with regulatory approved dosing schedules for PCSK9i mAb within the ASCVD population taking MTD statins.

Methods

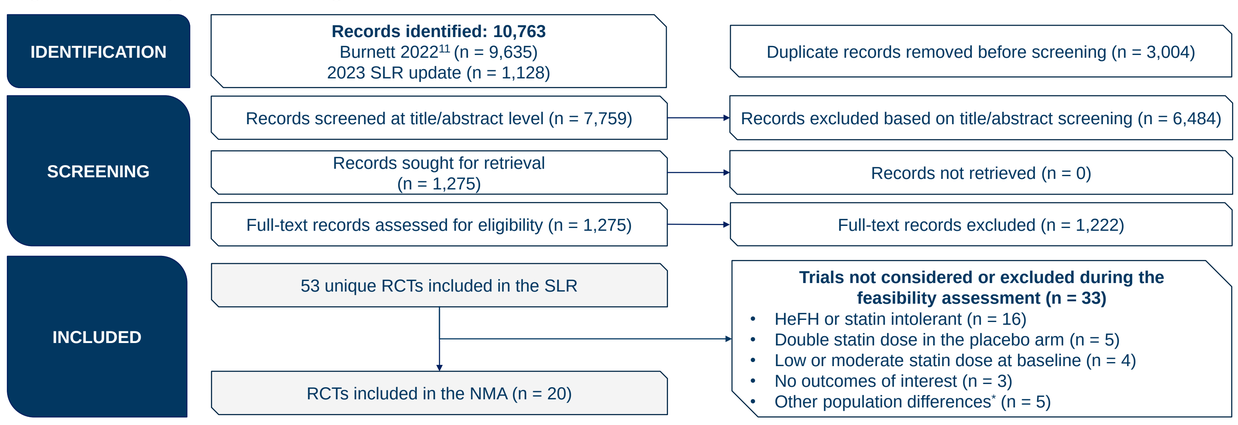
Study identification

- A systematic literature review (SLR) was conducted through January 2023 using OvidSP® (MEDLINE® and Embase®), Cochrane®, PubMed®, and Web of Science™ databases to identify published randomized clinical trials (RCTs) for approved non-statin LLT drugs. **Figure 1** presents a summary of study selection.

Study selection

- Trial evidence among patients with hypercholesterolemia and/or increased CVD risk (including ASCVD) was assessed for feasibility of indirect comparison with inclisiran.
- In addition to Q2W dosing for PCSK9i mAb assessed in the NMA by Burnett et al. 2022[11], monthly (QM) dosing regimens for PCSK9i mAb (evolocumab 420 mg QM and alirocumab 300 mg QM) were also included in this updated analysis.
- Fifty-three RCTs evaluating comparators and outcomes of interest were assessed for feasibility using the following criteria:
  - Whether there was a connected network comparing the treatments and outcomes of interest.
  - Whether there were differences in study, patient, and outcomes characteristics which are likely modifiers of relative treatment effects.
  - Whether there were differences in methods of imputation used to handle missing data across the included trials.

Figure 1. Study selection diagram



Abbreviation: HeFH, heterozygous familial hypercholesterolemia; NMA, network meta-analysis; RCT, randomized controlled trial; SLR, systematic literature review.
*Patients with ASCVD or history of clinically significant CV disease were excluded; All patients underwent PCI.

Outcomes

- The primary outcome in our analysis was percentage (%) change in LDL-C from baseline to week 24 (or closest available time point).
- Most of the included trials used mixed-effects model repeated measures (MMRM) methods for assessment up to 24 weeks, and therefore post-hoc analyses of the ORION trials were conducted applying these methods to ensure that both the timepoint of assessment and methods used to handle missing data were comparable across trials.

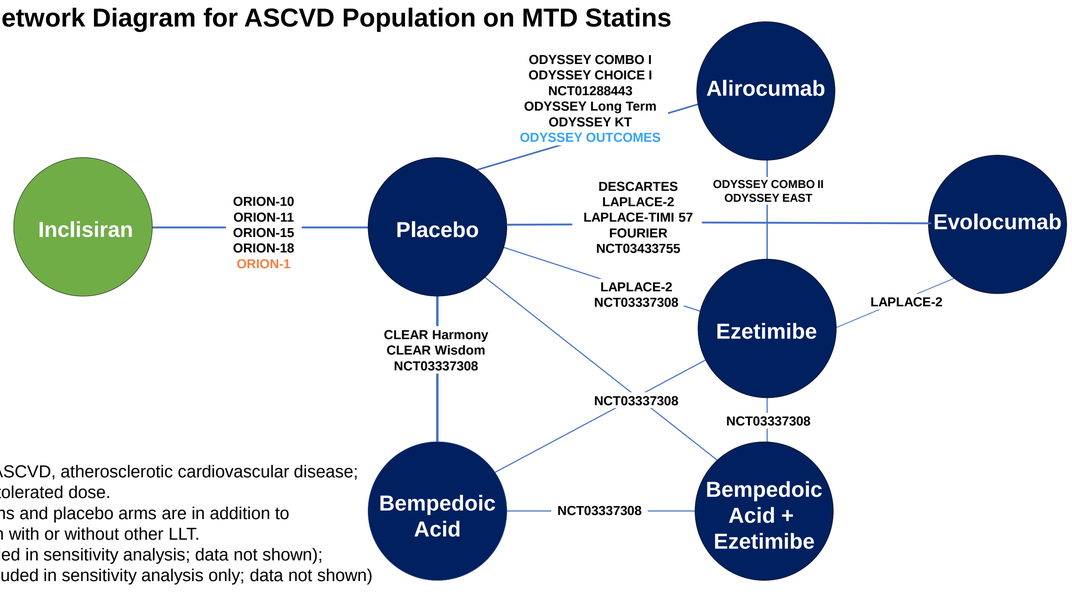
Statistical analysis:

- Random effects Bayesian NMA[12] was identified as the most appropriate method of analysis given the number of studies per comparison and observed heterogeneity in trial and patient characteristics.
- All Bayesian analyses were carried out via Markov Chain Monte-Carlo (MCMC) simulations (with 100,000 run-in, and 100,000 posterior), with a vaguely informative uniform prior for the random-effects SD and non-informative priors otherwise.
- Relative treatment effects were estimated as the mean differences (MD) with 95% credible intervals (CrI). Results with 95% CrIs that do not overlap zero were considered statistically significant.
- Model convergence and fit, statistical heterogeneity, and inconsistency were assessed.
- Analyses were conducted in Open BUGS (version 3.2.3).

Results

- The original NMA (Burnett et al. 2022)[11] considered the following population scenarios and included 23 trials in total:
  - **Base case**: ASCVD and/or high CV risk populations on MTD statins (n=17).
  - "**All-Comers" scenario**: All hypercholesterolemia, including ASCVD and HeFH and/or high CV risk populations on MTD statins (n=23).
- A total of 20 trials across inclisiran and other non-statin LLTs were deemed relevant for the analyses in the primary population of ASCVD. Analyses was not performed with HeFH and statin intolerant populations. **Figure 2** represents the network diagram of the included trials.

Figure 2. Network Diagram for ASCVD Population on MTD Statins

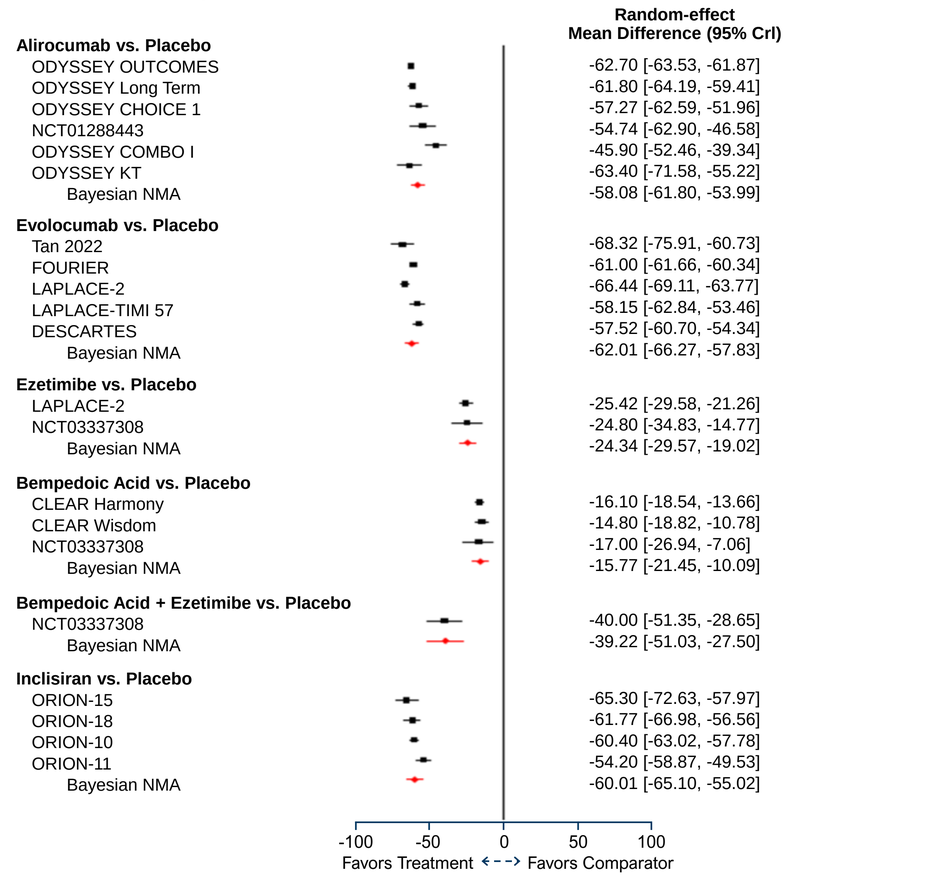


Abbreviations: ASCVD, atherosclerotic cardiovascular disease; MTD, maximally tolerated dose.
Note: Interventions and placebo arms are in addition to background statin with or without other LLT.
Blue text (excluded in sensitivity analysis; data not shown);
Orange text (included in sensitivity analysis only; data not shown)

Treatments vs. Placebo

- All treatments achieved a statistically significant reduction in LDL-C compared to the placebo **(Figure 3)**.

Figure 3: Difference in % Change in LDL-C in ASCVD Population on MTD Statins

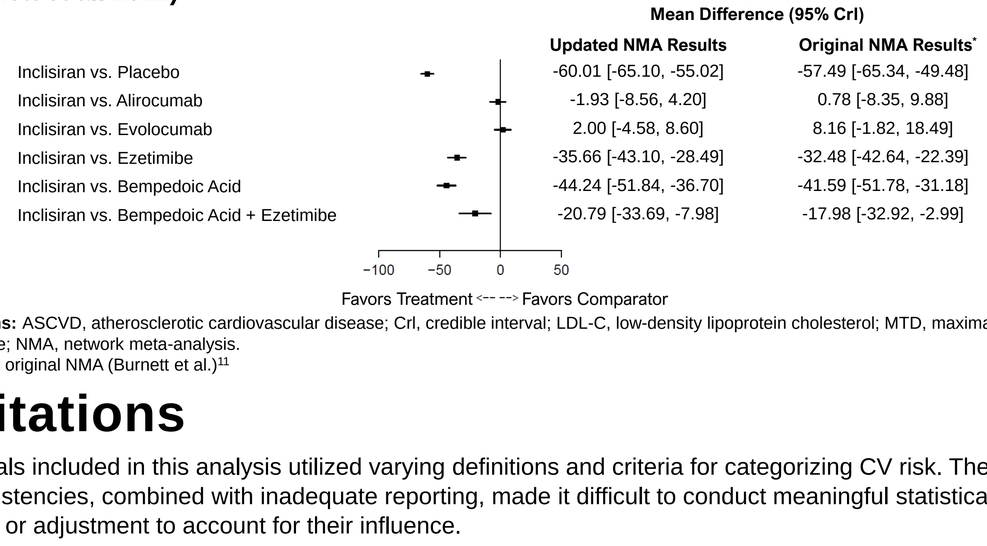


Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; NMA, network meta-analysis
Note: Red: Bayesian NMA results.

Inclisiran vs. Other Treatments

- Consistent with the findings from Burnett et al. 2022[11], inclisiran provided statistically significant LDL-C reduction compared to bempedoic acid (with or without ezetimibe) in our updated analysis **(Figure 4)**
  - Vs. Bempedoic acid: MD -44.24% (95% CrI: -51.84, -36.70)
  - Vs. Ezetimibe: MD -35.66% (95% CrI: -43.10, -28.49)
  - Vs. Bempedoic acid + Ezetimibe: MD -20.79% (95% CrI: -33.69, -7.98)
- Similar to the findings in Burnett et al. 2022[11], there was no significant difference in LDL-C reduction between inclisiran and PCSK9i mAb in our updated analysis **(Figure 4)**
  - Vs. Alirocumab: MD -1.93% (95% CrI: -8.56, 4.20)
  - Vs. Evolocumab: MD 2.00% (95% CrI: -4.58, 8.60)
- Moreover, the addition of new RCTs in our updated NMA resulted in all MD point estimates marginally moving in favor of inclisiran **(Figure 4)**; for example:
  - MD between inclisiran and evolocumab reduced from 8.16% (95% CrI: -1.82, 18.49) in Burnett et al. 2022[11] to 2.00% (95% CrI: -4.58, 8.60) in our updated analysis.
  - MD between inclisiran and alirocumab reduced from 0.78% (95% CrI: -8.35, 9.88) in Burnett et al. 2022[11] to -1.93% (95% CrI: -8.56, 4.20) in our updated analysis.
- Potential factors driving the observed shift in MD point estimates in favor of inclisiran (vs. PCSK9i mAb) relate to: 1) the inclusion of the recent ORION-15 and ORION-18 trials which observed slightly higher point estimates of the LDL-C reduction for inclisiran compared to ORION-10 and ORION-11, and 2) the inclusion of monthly dosing for evolocumab and alirocumab which are slightly less efficacious.

Figure 4: Difference in % Change in LDL-C in ASCVD Population on MTD Statins (Updated NMA and Burnett et al. 2022)



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; NMA, network meta-analysis.
*Results from original NMA (Burnett et al.)[11]

Limitations

- The trials included in this analysis utilized varying definitions and criteria for categorizing CV risk. These inconsistencies, combined with inadequate reporting, made it difficult to conduct meaningful statistical control or adjustment to account for their influence.
- While the NMA aimed to prioritize data available at week 24 and using MMRM as the imputation method, this was not available from all included trials. In these cases, the closest timepoint to 24 weeks was selected, as well as the next robust imputation method.

Conclusions

- This updated NMA reaffirms that inclisiran, alirocumab, and evolocumab are expected to provide similar clinically meaningful reduction in LDL-C in patients with hypercholesterolemia on MTD statins who are at increased CVD risk.
- Inclisiran is expected to deliver superior efficacy over placebo, bempedoic acid (with or without ezetimibe), and ezetimibe in reducing LDL-C.

Conflict of interest

Katharina Buesch, Ramandeep Jindal, Andreas Reichelt, Debajyoti Bhowmik and Harshul Nathani are employees of Novartis. Heather Burnett, Binod Neupane, Vicki Pierre, Kyle Fahrbach and Allie Cichewicz are employees of Evidera.

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References

1. NHS Digital; National Office Statistics, England 2023
2. NHS Digital 2018, Health Survey for England 2017, Adult Health Tables
3. Navar AM, et al. JAMA Cardiology 2017;2(11):1217-1225
4. Jaeger BC, et al. Hypertension 2019;73(2):327-334
5. Navar AM, et al. JAMA Cardiology 2019;4(4):375-379
6. Gitt AK, et al. Atherosclerosis 2016;255:200-209
7. Vos T, et al. The Lancet 2020;396(10258):1204-1222
8. Mach F, et al. European Heart Journal 2020;41(1):111-188
9. National Institute for Health and Care Excellence, Technology Appraisal Guidance [TA393] 2016
10. Lloyd-Jones MD, et al. Journal of the American College of Cardiology 2022;80(14):1366-1418
11. Burnett H, et al. Current Medical Research and Opinion 2021;38(5):777-784
12. Dias S, et al. NICE commissioned report 2011

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