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Impact of inclusion of drug adherence on cost effectiveness of inclisiran in atherosclerotic cardiovascular disease (ASCVD) patients

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KEY FINDINGS & CONCLUSIONS

- Inclusion of drug adherence in the cost-effectiveness modeling framework led to inclisiran becoming dominant (less costly, more effective) against both alirocumab and evolocumab.
- ASCVD is a chronic condition that often necessitates long-term, multi-drug therapy. In this context, patient adherence to prescribed treatments emerges as a pivotal factor influencing both clinical outcomes and the economic value of interventions. Incorporating real-world adherence rates into cost-effectiveness models provides a more robust and realistic assessment of therapeutic value.
- These findings underscore the importance of prioritizing therapies with higher adherence rates, as they not only enhance patient outcomes but also optimize the efficient use of healthcare resources.

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INTRODUCTION

- Real-world adherence to therapy plays a major role in treatment effectiveness, yet cost-effectiveness analyses based on clinical trial data often overlook this critical factor.
- Outside of controlled trials, therapy adherence can be suboptimal. Inclusion of adherence into a cost-effectiveness analysis strengthens the robustness of the health economic studies.[1]
- Adherence is especially critical in managing chronic conditions due to extended duration of usage of medication.[2] ASCVD is one such chronic condition where statins form the primary mainstay of therapy, but their usage has been plagued with low adherence levels.[3,4]
- Newer injectable lipid-lowering therapies have come up in recent years which are given as add-ons to statin therapy but do not require daily usage. Inclisiran has a twice-yearly dosing schedule after an initial 3-month dose while PCSK9 inhibitors (PCSK9is) are given biweekly or monthly.[5-7]
- Although PCSK9is and inclisiran have produced greater low density lipoprotein cholesterol (LDL-C) reductions in trials compared to statins [8-10], their real-world impact on LDL-C reduction (with adherence considered) and consequently the cost-effectiveness, remains unassessed.
- This analysis incorporated adherence rates into a previously published cost-effectiveness model and calculated incremental cost-effectiveness ratios (ICERs) for inclisiran compared to PCSK9is when used as adjunct therapies with statins and ezetimibe, or statins alone.

OBJECTIVE

This study evaluated how adherence affects the cost-effectiveness of inclisiran compared with PCSK9is alirocumab and evolocumab in ASCVD patients.

METHODS

A: Adherence calculation:

- This analysis used data from a published poster which analyzed US Komodo Healthcare data for proportion of patients in different adherence categories.[11] Komodo Health is a nationally representative longitudinal database that encompasses >150 national payers and captures 330 million patients and over a billion de-identified entries in the US from 2012 to present.
- The adherence categories were based on the percentage of days covered (PDC) by the treatment: high adherence (PDC ≥80%), intermediate adherence (PDC 50%-79%), and low adherence (PDC ≤50%). The days of supply (DOS) for inclisiran was assumed to be 92 + 90 days for the 1st dose and 183 + 90 days for the subsequent doses, by incorporating an allowable 90-day window around the expected dose. Similarly, the DOS for alirocumab and evolocumab was assumed to be 31 + 7 days for monthly dosing (per prescribing information).
- The data demonstrates that patients on inclisiran had higher levels of adherence compared to those on PCSK9is (**Table 1**).

Table 1: Proportion of patients by adherence categories for inclisiran and PCSK9is

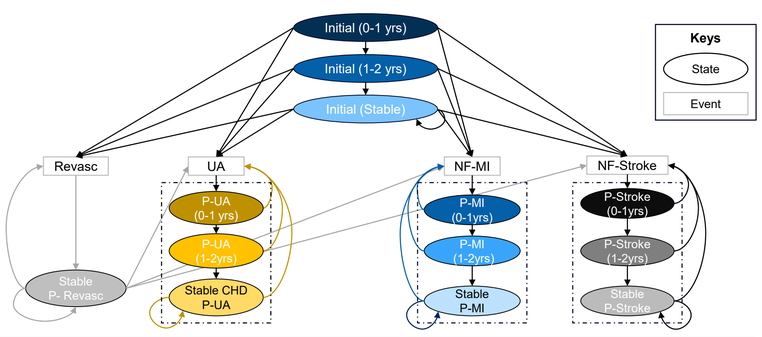
Adherence (%) category	Inclisiran	PCSK9is
PDC ≥80	79.0%	56.0%
PDC 50–79	11.9%	16.9%
PDC ≤50	9.1%	27.1%

Abbreviations: PDC: percentage of days covered

B. The Cost effectiveness model:

- The analysis utilized a Markov model (**Figure 1**) based on a previous submission to National Institute for Health and Care Excellence (NICE) from the England and Wales payer perspective.
- The model used Phase 3 clinical trial data from ORION-10, ORION-11, ORION-15 and ORION-18 trials.
- The model was built over a lifetime horizon, assuming a maximum age of 100 years. Costs and outcomes were discounted at an annual rate of 3.5%.
- The baseline risks for the ASCVD population were derived from an analysis of Clinical Practice Research Datalink (CPRD) [12,13] The change in LDL-C was translated into risks by using Cholesterol Treatment Trialists (CTT) meta-analysis.[14]
- The LDL-C reduction was modeled using data from the Network Meta-Analysis (NMA) conducted by Burnett, et al. (2022) which used clinical trial data.[15]
- The cost-effectiveness model then estimated the incremental cost-effectiveness ratio as shown in **Figure 2**.

Figure 1: Markov structure for the Cost-Effectiveness model



Logical further CV events including Revasc, UA, NF-MI, and NF-stroke. Transitions only allowed if moving into a worse event (UA → MI → Stroke). All patients are at a risk of CV or non-CV death.

Abbreviations: Revasc: Revascularisation, UA: Unstable Angina, MI: Myocardial Infarction

Figure 2: Cost-Effectiveness model workflow

Population
(baseline risks are taken from analysis of CPRD for ASCVD population)[10]

Administer drugs

Change in LDL-C

Translating changes in LDL-C to changes in risk (CTT meta-analysis)[12]

Number of events

MI, stroke, Revascularisation, CV death, UA, Non-CV death

Apply Utility and Costs

Incremental cost-effectiveness ratio (ICER) | Quality-adjusted life-years (QALYs)

Abbreviations: CPRD: Clinical Practice Research Datalink: ASCVD: atherosclerotic cardiovascular disease; CTT: Cholesterol Treatment Trialists, CV: Cardio-vascular, UA: Unstable Angina, MI: Myocardial Infarction

C. Adherence adjusted LDL-C reduction calculation:

- As patients in randomized clinical trials (RCTs) are adherent to their therapy, it was assumed that patients with a PDC of ≥ 80% would experience the same clinical outcomes as patients in RCTs. Thus, the LDL-C reduction predicted in a network meta-analysis (NMA) by Burnett, et al. (2022) was assumed to correspond to PDC ≥ 80% category.[15]
- In a study on statins by Vupputuri S, et al. (2016), the data for patients with a history of coronary heart disease or risk equivalent(s) taking statins from Kaiser Permanente Georgia was used to calculate the LDL-C reduction based on adherence for the 3 PDC categories. LDL-C level was assumed to reduce by same ratio for inclisiran and PCSK9is as estimated for statins by Vupputuri S, et al. (2016) for the intermediate and low adherence categories.[16]
- We estimated the adherence-adjusted LDL-C reduction for inclisiran and PCSK9is by applying weighted averages using population proportions from the Komodo Health database. The adherence adjusted LDL-C reduction is calculated using the formula:

$$\text{Adherence adjusted LDL-C reduction: } \sum(w_i.x_i)$$

Where:

w_i = Population proportion in each adherence category

x_i = LDL-C reduction in each adherence category

- The adherence adjusted LDL-C reduction estimated for inclisiran and PCSK9is were then incorporated into the cost-effectiveness (CE) model to estimate the Incremental Cost-Effectiveness Ratio (ICER).

D. Scenario Analysis:

A scenario was developed wherein adherence to PCSK9is was increased by 20% within the high adherence category. Adherence levels in the low and intermediate categories were proportionally adjusted to maintain their original distribution. The adherence rate for inclisiran remained unchanged. The adherence adjusted LDL-C reduction was estimated and then incorporated into the CE model to estimate the Incremental Cost-Effectiveness Ratio (ICER).

RESULTS

- An adjustment factor was established based on statin use. It was observed that patients with intermediate adherence to statins achieved an LDL-C reduction of 32.7%, whereas those with high adherence achieved 42.3%. This represents a 22.7% relative reduction in treatment effect for the intermediate adherence group. This adjustment factor of 22.7% was applied to the LDL-C reductions reported in the Burnett et al. (2022)[15] network meta-analysis—which were 58.08% for alirocumab, 62.01% for evolocumab, and 60.01% for inclisiran. This resulted in estimated adherence-adjusted LDL-C reductions of 44.9% for alirocumab, 47.94% for evolocumab, and 46.39% for inclisiran.
- The process was repeated for the low adherence category. It was determined that the LDL-C reduction with statins in this group was 52.6% less than that of the intermediate group. Accordingly, intermediate adherence estimates were reduced for alirocumab, evolocumab, and inclisiran by 52.6%, resulting in the final values of 21.28%, 22.27%, and 21.99%, respectively (**Table 2**).

Table 2: Estimation of adherence adjusted LDL-C reduction for ASCVD population by inclisiran and PCSK9is for PDC 50%-79% and PDC ≤50%

Drug	Vupputuri S, et al. (2016) [11]		Alirocumab	Evolocumab	Inclisiran	Data Source for PCSK9is and Inclisiran
% decrease in LDL-C by adherence levels			% decrease in LDL-C by adherence levels			
PDC ≥80%	42.3	⇩ 22.7 % ⇩	58.08	62.01	60.01	Burnett, et al. (2022)[10]
PDC 50%-79%	32.7	⇩ 52.6 % ⇩	44.9	47.94	46.39	Calculated
PDC ≤50%	15.5		21.28	22.72	21.99	Calculated

Abbreviations: PDC: Proportion of days covered

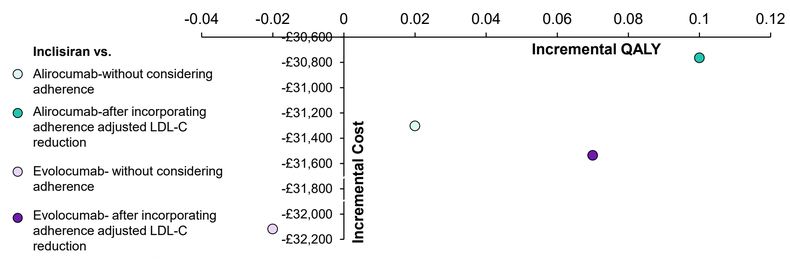
- The effectiveness of inclisiran and PCSK9 inhibitors in reducing LDL-C was calculated based on the proportion of population in each adherence category. Adherence-adjusted LDL-C reduction for inclisiran was 54.92%, compared to 62.01% estimated by NMA — a difference of 7.09%. For alirocumab and evolocumab, the adherence-adjusted LDL-C reduction values showed a difference of 21%, resulting in reductions of 45.88% and 48.98%, respectively. These estimates were utilized as inputs in the CE model (**Table 3**).

Table 3: Estimated adherence adjusted LDL-C reduction for inclisiran and PCSK9is for ASCVD population

	Inclisiran	Alirocumab	Evolocumab
Adherence adjusted percent LDL-C reduction for ASCVD population	54.92	45.88	48.98

- For ASCVD population, without adherence adjustment, inclisiran was dominant (less costly, more effective) over alirocumab, with a QALY gain of 0.02 and £31,303 in cost offsets. Compared to evolocumab, inclisiran had an incremental QALY of -0.02 and had a cost offset of £32,119. After adherence adjustment, for the ASCVD population, inclisiran was dominant (less costly, more effective) over both, gaining 0.1 QALYs vs. alirocumab and 0.07 vs. evolocumab, with cost offsets of £30,763 and £31,536, respectively. The visual representation before and after adherence adjustment is presented in CE plane in **Figure 3** and the details are presented in **Table 4**.

Figure 3: Cost-effectiveness plane before and after incorporating adherence for ASCVD population over a lifetime horizon



Abbreviations: ASCVD: atherosclerotic cardiovascular disease, QALY: Quality-adjusted life year

Table 4: Results before and after adherence adjustment for ASCVD population over a lifetime horizon

Population	Molecule	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Incremental ICER (€/QALY)
ASCVD- without considering adherence	Inclisiran	23,885	8.28			
	Alirocumab	55,188	8.26	-31,303	0.02	Inclisiran is dominant
	Evolocumab	56,004	8.30	-32,119	-0.02	1,532,167
ASCVD – after incorporating adherence adjusted LDL-C reduction	Inclisiran	23,859	8.22			
	Alirocumab	54,622	8.12	-30,764	0.10	Inclisiran is dominant
	Evolocumab	55,395	8.15	-31,536	0.07	Inclisiran is dominant

Note: Inclisiran is dominant represents that inclisiran is less costly and more effective
Abbreviations: QALY: Quality-adjusted life year

Results of Scenario Analysis

- The adherence levels for PCSK9is applied in the scenario analysis wherein adherence to PCSK9is was increased by 20% are shown in **Table 5**. The high adherence category distribution for PCSK9is increased from 56% to 67.2% and then used in the cost-effectiveness model.

Table 5: Adherence distribution for PCSK9is applied in the scenario

Adherence distribution	PCSK9is
PDC ≥80%	67.2%
PDC 50% - 79%	12.6%
PDC ≤50%	20.2%

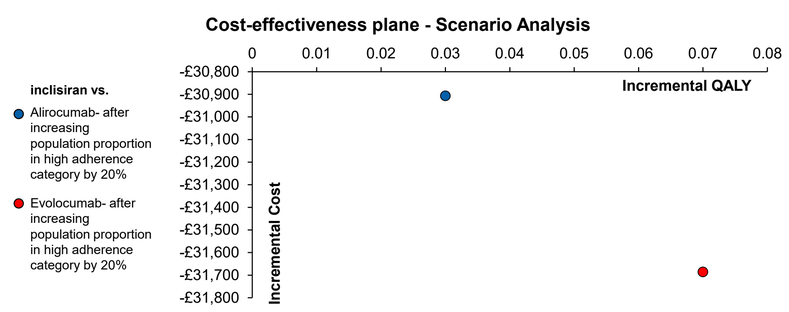
- With updated adherence distribution, inclisiran was less costly and more effective when compared to both alirocumab and evolocumab in the ASCVD population. (**Table 6**). The CE plane is presented in **Figure 4**.

Table 6: Results after increasing high adherence category population proportions by 20% for PCSK9is for ASCVD population over a lifetime horizon

Population	Molecule	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Incremental ICER (€/QALY)
ASCVD	Inclisiran	23,859	8.221			
	Alirocumab	54,766	8.191	-30,907	0.03	Inclisiran is dominant
	Evolocumab	55,545	8.155	-31,686	0.07	Inclisiran is dominant

Note: Inclisiran is dominant represents that inclisiran is less costly and more effective
Abbreviations: QALY: Quality-adjusted life year

Figure 4: Cost-effectiveness plane for scenario analysis (20% increased proportion of population in high adherence category for PCSK9is) for ASCVD population over a lifetime horizon



Abbreviations: ASCVD: atherosclerotic cardiovascular disease, QALY: Quality-adjusted life year

Discussion

Inclisiran was less costly and more effective than alirocumab both when adherence was excluded and included in the CE model. The incremental benefit of QALYs and costs increased in magnitude after including adherence. With evolocumab, the results indicated that inclisiran became less costly and more effective after adjusting for adherence.

The analysis had certain limitations. It did not account for implication of adherence on drug costs, primarily due to the paucity of data. However, the results from the scenario analysis showed that the results would likely have not changed even after accounting for this. The adherence levels were also assumed to be sustained throughout the lifetime of the patient. However, since this assumption was common across both arms, this would likely not have changed the results.

As the adherence estimates were based on a representative US population, further analysis using adherence data from other countries would be required to understand how cost-effectiveness varies in other cases.

The analysis had several strengths – the incorporation of adherence was done using estimates from the Komodo database, which due to its nationally representative sample size, was a robust source for the adherence estimates. Additionally, the use of a well-established cost-effectiveness model that has been reviewed across multiple health technology assessment (HTA) bodies further strengthens the robustness of this analysis.

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