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CO140

Impact of pharmacotherapy adherence on the reduction of major adverse cardiovascular events (MACE) among atherosclerotic cardiovascular disease (ASCVD) patients

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KEY FINDINGS & CONCLUSIONS

- For a cohort of 100,000 patients, inclisiran prevented 4,517 additional MACE events over alirocumab and 3,006 over evolocumab for a lifetime horizon.
- In the evaluation of lipid-lowering therapies for ASCVD, medication adherence is an important driver of both clinical and economic outcomes. This analysis demonstrates that interventions with higher levels of real-world adherence—such as inclisiran—yield enhanced prevention of major adverse cardiovascular events (MACE), thereby maximising clinical effectiveness and health gains at the population level.
- Therapies like inclisiran with better adherence profiles compared to PCSK9is should be considered by stakeholders including clinicians, payers, policymakers, and health technology assessment bodies to optimise health-related quality of life, health outcomes and cost-effectiveness.

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INTRODUCTION

- Pharmacotherapy adherence is a critical determinant of clinical outcomes. While randomised controlled trials (RCTs) often report high adherence rates and robust efficacy of lipid-lowering therapies, real-world adherence is frequently suboptimal, potentially diminishing the effectiveness of these interventions compared to controlled trial settings.[1]
- This discrepancy is particularly important in the context of ASCVD, where effective lowering of low-density lipoprotein cholesterol (LDL-C) is essential for reducing the risk of major adverse cardiovascular events (MACE).[2]
- Current clinical guidelines recommend additional lipid-lowering therapies for ASCVD patients who do not achieve target LDL-C levels with maximally tolerated statins. Among these, inclisiran is a small interfering RNA therapy administered subcutaneously twice yearly after an initial and a 90-day dose. Other therapies include PCSK9 inhibitors (PCSK9is) such as alirocumab and evolocumab which are administered subcutaneously every two to four weeks.[3-5] The differences in dosing schedules between these therapies may have direct implications for patient adherence in real-world settings.
- Variations in adherence are likely to influence the degree of LDL-C reduction observed outside of clinical trial environments, thereby impacting cardiovascular outcomes.
- Despite the clinical relevance of these observations, there are limited studies which directly assessed the impact of real-world adherence differences between inclisiran and PCSK9 inhibitors on LDL-C lowering among ASCVD patients.
- This analysis incorporated adherence rates into cost-effectiveness modelling and calculated the MACE events for inclisiran compared to PCSK9 inhibitors when used as adjunct therapies with statins and ezetimibe, or statins alone.

OBJECTIVE:

This study evaluated the impact of real-world adherence on the prevention of MACE events among ASCVD patients.

METHODS

A: Adherence calculation:

- This analysis used data from a published poster which analyzed the US Komodo Health database for proportion of patients in different adherence categories.[6] Komodo Health is a nationally representative longitudinal database that encompasses >150 national payers and captures 330 million patients in the US from 2012 to present. It includes billions of de-identified clinical, pharmacy, and laboratory encounters, and both open and payer-complete profiles.
- 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 were 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 US Komodo Health data demonstrates that patients on inclisiran had higher levels of adherence compared to those on PCSK9is (**Table 1**).

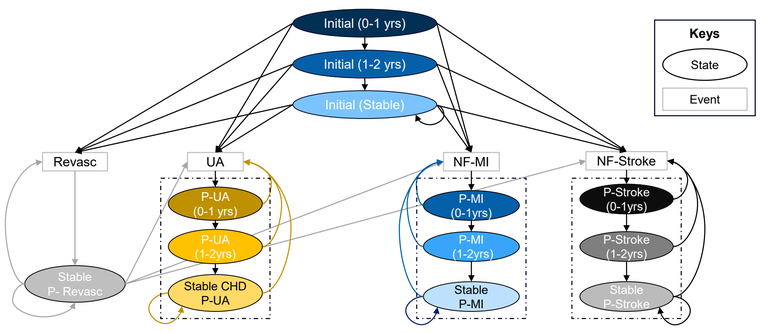
Table 1: Proportion of patients by adherence categories for inclisiran and PCSK9is

Adherence (%) category	Inclisiran	PCSK9is
PDC ≥80	79%	56%
PDC 50–79	11.9%	16.9%
PDC ≤50	9.1%	27.1%

B. The Cost effectiveness model:

- A Markov model, illustrated in Figure 1, forms the foundation of the analysis. This framework was based on a prior submission to the National Institute for Health and Care Excellence (NICE) and reflects the payer perspective for England and Wales. The model integrated Phase 3 clinical trial findings from ORION-10, ORION-11, ORION-15, and ORION-18.
- The model was built over a lifetime time horizon, assuming a maximum age of 100 years. Costs and outcomes were discounted at an annual rate of 3.5%.
- Baseline risks for individuals with ASCVD were sourced from the Clinical Practice Research Datalink (CPRD).[7, 8]
- Changes in LDL-C levels were mapped to risk estimates using the Cholesterol Treatment Trialists (CTT) meta-analysis.[9]
- LDL-C reductions were estimated based on findings from a Network Meta-analysis (NMA) by Burnett et al. (2022), which utilized data from clinical trials.[10]

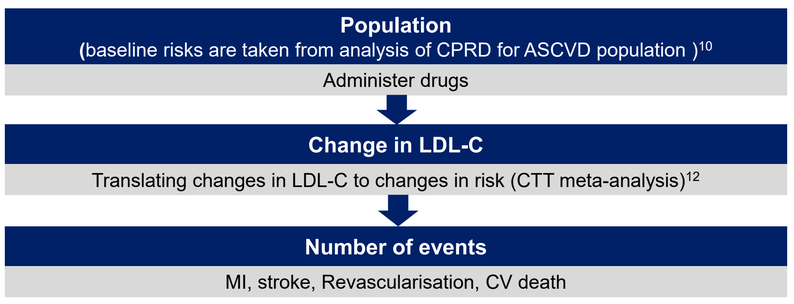
Figure 1: Markov structure for the Cost-Effectiveness model



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 for MACE event calculations



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 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 projected by Burnett et al. (2022) was considered representative of the outcomes expected in patients with a PDC of 80% or higher.[10]
- The reduction in LDL-C levels for inclisiran and PCSK9 inhibitors was assumed to be proportional to that observed for statins, as determined by Vupputuri S, et al. (2016) across intermediate and low adherence categories.[11] This study utilized data from members of Kaiser Permanente Georgia with established coronary heart disease or risk equivalents who were receiving statin therapy and were to quantify LDL-C reduction within three distinct PDC categories. Kaiser Permanente Georgia (KPGA) is an integrated healthcare delivery system serving approximately 235,000 members in the greater metropolitan Atlanta area. KPGA maintains comprehensive electronic medical records (EMRs) and other electronic databases of their members' health services utilization.
- 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:

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

Where:

w_i = Population proportion in each adherence category

x_i = LDL-C reduction in each adherence category

- The adherence adjusted LDL-C reduction levels for each molecule were then incorporated into the cost-effectiveness (CE) model to estimate the number of MACE events among patients taking Standard of Care (SoC), inclisiran and PCSK9is.
- The number of events prevented by inclisiran, alirocumab, and evolocumab was calculated in comparison to SoC, which included patients treated with statins, with or without ezetimibe.

D. Scenario Analysis:

- A scenario was created where the number of patients taking PCSK9is in the high adherence group were increased by 20%. The numbers in the low and medium groups were adjusted so that their overall proportion stayed the same. The adherence for inclisiran did not change. After these changes, the adherence-adjusted LDL-C levels were calculated and used in the cost-effectiveness model to estimate MACE events could be prevented by inclisiran and PCSK9is compared to SoC.

RESULTS

A. LDL-C reduction

- An adjustment factor was established based on statin use. We 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)[10] 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, respectively.
- 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 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

- In the ASCVD population, the reduction in LDL-C efficacy is less pronounced with inclisiran compared to PCSK9 inhibitors. Specifically, the LDL-C reduction achieved with inclisiran decreased by 8.5%, whereas reductions for alirocumab and evolocumab declined by 21% relative to the values reported in the network meta-analysis (NMA). These adherence-adjusted values were incorporated as inputs in the cost-effectiveness model, replacing the NMA-derived estimates for calculations accounting for adherence (**see Table 3**).

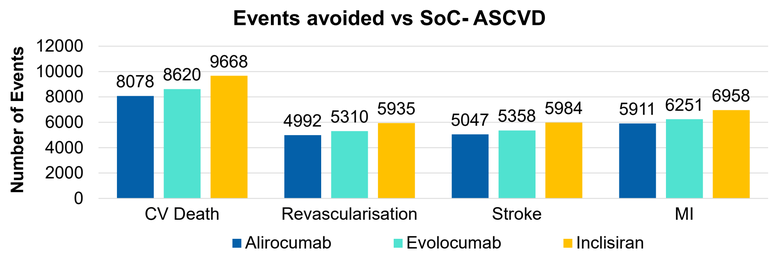
Table 3: Estimated LDL-C reduction for inclisiran and PCSK9is for ASCVD and HeFH population

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

B. Reduction in MACE events

- For a cohort of 100,000 patients, lifetime MACE events were estimated to be 112,892, 117,409, and 115,898, respectively for inclisiran, alirocumab and evolocumab. It was estimated that inclisiran prevents an additional 1,590 cardiovascular deaths, 943 revascularization cases, 937 strokes, and 1,047 myocardial infarctions compared to alirocumab. When compared to evolocumab, inclisiran was estimated to prevent an additional 1,048 cardiovascular deaths, 625 revascularization cases, 626 strokes, and 707 myocardial infarctions. Overall, inclisiran prevented 4,517 additional MACE events over alirocumab and 3,006 over evolocumab. Details are presented in **Figure 3**.

Figure 3: ASCVD- additional events prevented vs. SoC per 100,000 patients over a lifetime horizon



Abbreviations: CV: Cardio-vascular, MI: Myocardial Infarction, SoC: Standard of care

C. Scenario Analysis Results

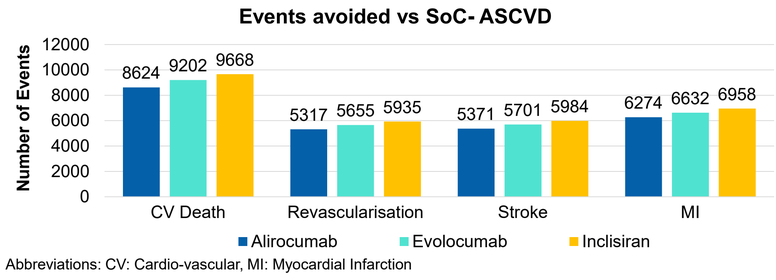
- The proportion of patients in the high adherence category was increased by 20% for PCSK9is, resulting in an increase from 56% to 67.2%. These values were then used in the cost-effectiveness model. The values are shown in **Table 4**.

Table 4: Adherence distribution for PCSK9is applied in the scenario analysis (20% increase in high adherence category patients for PCSK9is)

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

- With the updated distribution of proportion of patients in different adherence categories, for the ASCVD population, inclisiran prevented an additional 1,044 cardiovascular deaths, 618 revascularization cases, 613 strokes, and 684 myocardial infarctions compared to alirocumab. When compared to evolocumab, inclisiran prevented an additional 466 cardiovascular deaths, 280 revascularization cases, 283 strokes, and 326 myocardial infarctions (**Figure 4**).

Figure 4: ASCVD- additional events prevented vs. SoC per 100,000 patients after incorporating 20% increased proportion to high PDC category for PCSK9is over a lifetime horizon



Abbreviations: CV: Cardio-vascular, MI: Myocardial Infarction

Discussion

This analysis underscores the critical role of medication adherence in understanding clinical outcomes among patients treated with lipid-lowering therapies, particularly in the context of ASCVD population.
By incorporating real-world adherence data into MACE outcomes analysis, we estimated that inclisiran has a higher adherence-adjusted LDL-C reduction compared to PCSK9is. This resulted in a greater number of cardiovascular events prevented, i.e. inclisiran was associated with a reduction of additional cardiovascular deaths, revascularization procedures, strokes, and myocardial infarctions when compared to both alirocumab and evolocumab.
It is important to acknowledge several limitations of this analysis. The proportional reduction in LDL-C for inclisiran and PCSK9 inhibitors was assumed to mirror that observed with statins. However, a study which captures both adherence levels and LDL-C reduction for inclisiran and PCSK9is should be preferred and prioritized in future analyses to make these estimates more robust. Moreover, the model assumes that adherence observed at one year remains stable throughout the patient's lifetime, an assumption that warrants validation through long-term studies. However, since this assumption was common across both arms, this would likely not have changed the results.
The analysis had several strengths – the incorporation of adherence was done using estimates from the Komodo database, which due its nationally representative sample size, was a robust source for the adherence estimates. To further enhance the reliability and generalizability of these findings, future research should incorporate adherence data from diverse sources and regions.
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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