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Poster CO85

Effectiveness of Inclisiran and Evolocumab in LDL-C Goal Attainment - A Hybrid Decision Tree-Markov Model Analysis

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KEY FINDINGS & CONCLUSIONS

- Inclisiran demonstrates consistently lower NNT values across all time points, indicating superior long-term effectiveness in achieving LDL-C targets compared to Evolocumab.
- The divergence becomes more pronounced after Year 2, suggesting better persistence and durability of response with Inclisiran.

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INTRODUCTION

- Managing LDL cholesterol (LDL-C) is directly linked to atherosclerotic cardiovascular disease (ASCVD) event risk. LDL-C is not just a biomarker—it is a modifiable causal factor. Lowering LDL-C consistently and maintaining targets over the long term is essential to reduce ASCVD event risk [1-3].
- ESC/EAS (2019) emphasize “the lower, the better, for longer” principle for LDL-C, especially in very-high-risk patients (target <55 mg/dL), because residual risk persists even after initial lowering and thus management of ASCVD should strive to obtain sustained LDL-C reduction over years as it leads to cumulative risk reduction [4].
- Long-term sustained LDL-C reduction—and therefore long-term ASCVD risk reduction—depends on several interrelated factors, with persistence to treatment being one of the most critical as treatment effect with current available therapies is reversible: when treatment stops, LDL-C rebounds rapidly, often within weeks, erasing prior gains [5].
- Health decision-making should then consider the potential real-world impact of treatments on patient outcomes, translating complex statistical outcomes into simple and clinically meaningful metric and, hence, facilitating interpretation by clinicians, policymakers, and patients.
- The number needed to treat (NNT) provides an intuitive estimate of absolute intervention benefit, quantifying how many patients must receive a given intervention for one additional patient to achieve the desired outcome [6].

OBJECTIVE

This study aims to estimate the NNT of inclisiran and evolocumab in achieving LDL-C target levels (2019 ESC/EAS guidelines) [4].

METHODS

A hybrid decision tree-Markov model was employed to simulate the proportion of responders over a 5-year time horizon. Decision-tree transition probabilities were calculated based on the proportion of patients achieving LDL-C target levels. Conditional on the response status, the Markov model assumed three mutually exclusives health states: Responders on treatment, non- responders off treatment and non responder *ad-initio*. Treatment persistence was modelled adjusting exponential distributions on discontinuation rates. The proportion of patients achieving LDL-C target and the discontinuation rates were retrieved from real-world data. The number needed to treat was calculated using the following formula [6]:

$$NNT_i = \frac{1}{Absolute\ Risk\ Reduction\ (ARR)_i}, \text{ where } ARR = CER_i - EER_i \text{ at year i =1 to 5}$$

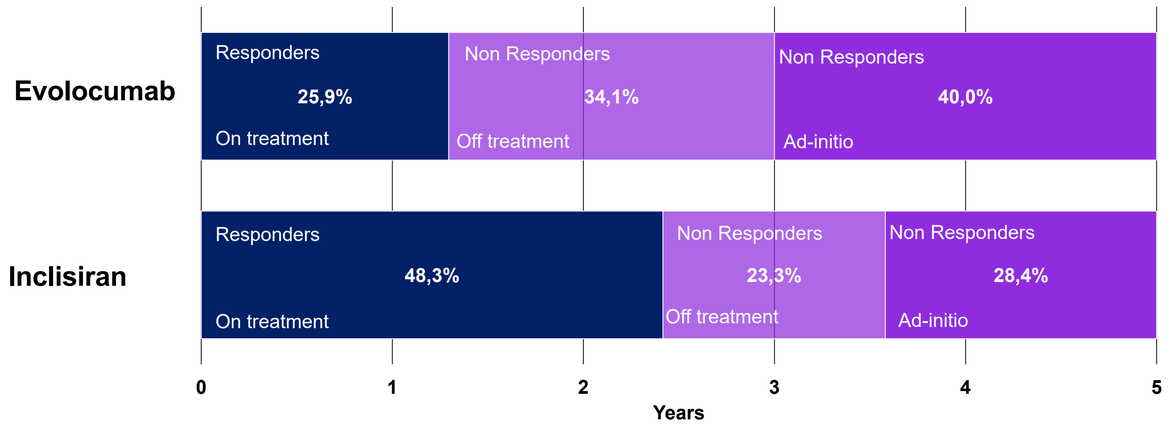
CER: Proportion of patients achieving LDL-C targets under standard care.
EER: Proportion of patients achieving LDL-C targets with PCSK9 inhibitor therapy (evolocumab or inclisiran).

Two-way deterministic sensitivity was performed to assess the impact of parameter uncertainty.

RESULTS

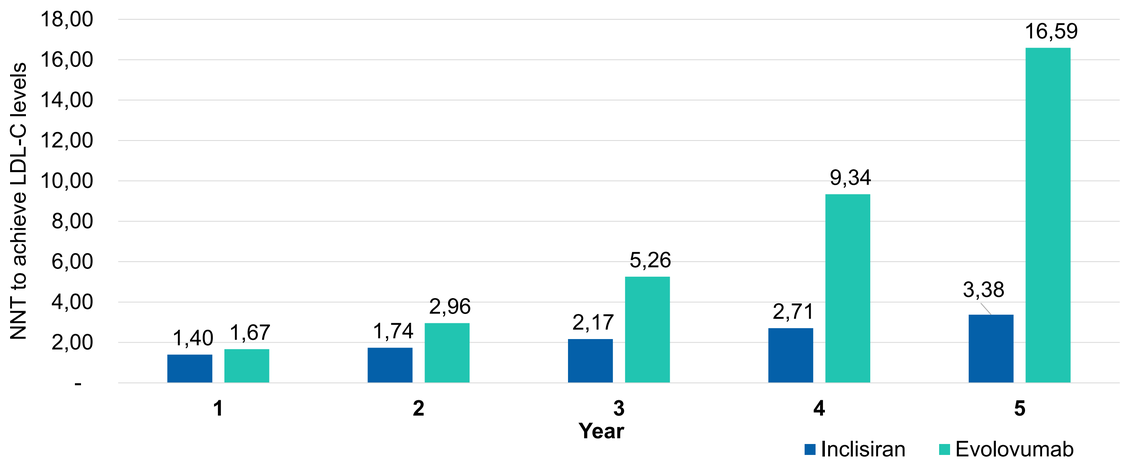
- Observational data reports that 71.6% of patients treated with inclisiran (VICTORION-Initiate) [7] achieve LDL-C goals and a discontinuation rate per year of 19.8% [8]. For evolocumab, observational data demonstrated that 60% of patients treated with evolocumab (Heymans study) [9] achieve LDL-C goals. Based on reported literature, the discontinuation rate assumed per year was 43.7%.
- Over the 5 years of the time horizon, nearly half of the cohort with inclisiran remains as responders while on treatment (accounting for 2.41 person-years), whereas with evolocumab only about one-quarter (25.9%) of the cohort remains responder while on treatment, spending 1.3 person-years on that health state.

Figure 1. Cohort distribution per health state



- Figure 2 shows the NNT to achieve LDL-C target levels over five years for inclisiran (blue) and evolocumab (green).
- Across the time horizon, inclisiran consistently maintains lower NNT values, starting near 1.4 in Year 1 and gradually increasing to 3.38 by Year 5. This indicates sustained effectiveness and persistence in achieving LDL-C targets.
- In contrast, evolocumab begins with an NNT of 1.67 in Year 1 but rises sharply over time, reaching 16.59 by Year 5. This trend suggests a significant decline in treatment effectiveness, driven by discontinuation.

Figure 2. Number needed to treat with achieve LDL-target levels EAS/ESC



- Table 1 summarizes the incremental differences in NNT between evolocumab and inclisiran based on absolute difference (Δ) and ratios
- In Year 1, the difference is minimal (Δ 0.27), with evolocumab requiring 1.91 times more patients than inclisiran. By Year 2, the gap widens to Δ 1.22 (ratio 1.70), and in Year 3, evolocumab requires 2.42 times more NNT patients. In Year 4, the difference reaches Δ 6.63, with a ratio of 3.45, and by Year 5, evolocumab's NNT is nearly five times higher (ratio 4.95) than inclisiran's, with an absolute difference of 13.21.

Table 1. Incremental results (evolocumab versus inclisiran) over 5 year time horizon

Evo Vs Incl	Year 1	Year 2	Year 3	Year 4	Year 5
Abs Diff	0.27	1.22	3.09	6.63	13.21
Ratio	1.91	1.70	2.42	3.45	4.95

Deterministic Two- Way Sensitivity Analysis

- Two-way deterministic sensitivity analysis was performed assuming that a ± 20% variation to explore the combined impact of uncertainty in the two key parameters: proportion of response on achieving LDL-C levels (rows) and discontinuation rates (coloumns). Year 2 and Year 5 were the cut-offs precluded – see Table 2 and Table 3 for inclisiran and evolocumab, respectively.
  - For Year 2, inclisiran's NNT values range from 1.37 (high response, low discontinuation) to 2.29 (low response, high discontinuation) (base case at 1.74).
  - For Year 5, inclisiran's NNT values range from 2.29 to 5.17, with the base case at 3.38. Lower discontinuation and higher response rates consistently reduce NNT, while higher discontinuation and lower response rates increase NNT.

Table 2. Two-way sensitivity analysis for inclisiran's NNT

		Discontinuation Rate																			
LDL-C response rate	**Inclisiran**	**-20%**	**-15%**	**-10%**	**-5%**	**0%**	**5%**	**10%**	**15%**	**20%**		**-20%**	**-15%**	**-10%**	**-5%**	**0%**	**5%**	**10%**	**15%**	**20%**
		16%	17%	18%	19%	20%	21%	22%	23%	24%		16%	17%	18%	19%	20%	21%	22%	23%	24%
-20%	57%	2.07	2.10	2.12	2.15	2.18	2.20	2.23	2.26	2.29		3.48	3.65	3.83	4.02	4.22	4.43	4.66	4.91	5.17
-15%	61%	1.95	1.98	2.00	2.02	2.05	2.07	2.10	2.13	2.16		3.28	3.43	3.60	3.78	3.97	4.17	4.39	4.62	4.86
-10%	64%	1.84	1.87	1.89	1.91	1.93	1.96	1.98	2.01	2.04		3.09	3.24	3.40	3.57	3.75	3.94	4.15	4.36	4.59
-5%	68%	1.75	1.77	1.79	1.81	1.83	1.86	1.88	1.90	1.93		2.93	3.07	3.22	3.38	3.55	3.73	3.93	4.13	4.35
0%	72%	1.66	1.68	1.70	1.72	**1.74**	1.76	1.79	1.81	1.83		2.78	2.92	3.06	3.21	**3.38**	3.55	3.73	3.93	4.13
5%	75%	1.58	1.60	1.62	1.64	1.66	1.68	1.70	1.72	1.74		2.65	2.78	2.92	3.06	3.22	3.38	3.55	3.74	3.94
10%	79%	1.51	1.52	1.54	1.56	1.58	1.60	1.62	1.64	1.66		2.53	2.65	2.78	2.92	3.06	3.22	3.38	3.56	3.75
15%	83%	1.43	1.45	1.47	1.49	1.50	1.52	1.54	1.56	1.58		2.40	2.52	2.65	2.78	2.92	3.06	3.22	3.39	3.57
20%	87%	1.37	1.38	1.40	1.42	1.43	1.45	1.47	1.49	1.51		2.29	2.40	2.52	2.64	2.78	2.92	3.07	3.23	3.40
		Year 2										Year 5								

- For Year 2, evolocumab's NNT values range from 2.14 (high response, low discontinuation) to 4.38 (low response, high discontinuation). The base case (72% response, 20% discontinuation) is highlighted at 2.96.
- For Year 5, evolocumab's NNT values vary widely, from 7.76 to 40.72, with the base case at 16.59. Lower discontinuation and higher response rates reduce NNT, while higher discontinuation and lower response rates, as expected, substantially increase NNT.

Table 3. Two-way sensitivity analysis for evolocumab's NNT

		Discontinuation Rate																			
LDL-C response rate	**Evolocumab**	**-20%**	**-15%**	**-10%**	**-5%**	**0%**	**5%**	**10%**	**15%**	**20%**		**-20%**	**-15%**	**-10%**	**-5%**	**0%**	**5%**	**10%**	**15%**	**20%**
		35%	37%	39%	42%	44%	46%	48%	50%	52%		35%	37%	39%	42%	44%	46%	48%	50%	52%
-20%	48%	3.20	3.31	3.43	3.56	3.70	3.85	4.01	4.19	4.38		11.64	13.35	15.38	17.81	20.74	24.29	28.65	34.02	40.72
-15%	51%	3.01	3.12	3.23	3.35	3.48	3.62	3.78	3.94	4.12		10.96	12.56	14.47	16.76	19.52	22.86	26.96	32.02	38.32
-10%	54%	2.85	2.95	3.05	3.17	3.29	3.42	3.57	3.72	3.89		10.35	11.86	13.67	15.83	18.43	21.59	25.46	30.24	36.19
-5%	57%	2.70	2.79	2.89	3.00	3.12	3.24	3.38	3.53	3.69		9.80	11.24	12.95	15.00	17.46	20.46	24.12	28.65	34.29
0%	60%	2.56	2.65	2.75	2.85	**2.96**	3.08	3.21	3.35	3.50		9.31	10.68	12.30	14.25	**16.59**	19.43	22.92	27.22	32.57
5%	63%	2.44	2.53	2.62	2.71	2.82	2.93	3.06	3.19	3.34		8.87	10.17	11.72	13.57	15.80	18.51	21.83	25.92	31.02
10%	66%	2.33	2.41	2.50	2.59	2.69	2.80	2.92	3.05	3.19		8.47	9.71	11.18	12.95	15.08	17.67	20.83	24.74	29.61
15%	69%	2.23	2.31	2.39	2.48	2.57	2.68	2.79	2.91	3.05		8.10	9.29	10.70	12.39	14.43	16.90	19.93	23.67	28.33
20%	72%	2.14	2.21	2.29	2.37	2.47	2.57	2.67	2.79	2.92		7.76	8.90	10.25	11.87	13.82	16.20	19.10	22.68	27.15
		Year 2										Year 5								

Discussion

- Inclisiran demonstrates superior long-term effectiveness in achieving LDL-C targets, maintaining consistently lower NNT values than evolocumab across all time points.
- Persistence to treatment is a key differentiator: nearly half of patients on inclisiran remain responders at five years, compared to only about a quarter on evolocumab, highlighting the impact of lower discontinuation rates.
- The gap in NNT widens over time: while initial differences are modest, by year five, evolocumab's NNT is nearly five times higher than inclisiran's, reflecting a significant decline in treatment efficiency with evolocumab
- The gap in NNT widens over time: While initial differences are modest, by year five, evolocumab's NNT is nearly five times higher than inclisiran's, reflecting a significant decline in treatment efficiency with evolocumab.
- RWE is essential for validating, contextualizing, and extending the findings from model-based analyses as adherence to LLT is a determinant factor impacting CV risk.

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Disclosures

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