Alirocumab PRALUENT and Cardiovascular Outcomes after Acute Coronary Syndrome[1]

ODYSSEY OUTCOMES Trial Summary

SUMMARY

The ODYSSEY OUTCOMES trial evaluated the efficacy of alirocumab, a PCSK9 inhibitor, in reducing cardiovascular (CV) events in patients who had experienced an acute coronary syndrome (ACS) within the past 1 to 12 months and were already on maximally tolerated statin therapy.

Bottom Line: Alirocumab, added to high-intensity statin therapy, provides additional protection against cardiovascular events in high-risk patients following an ACS. Alirocumab dose intensity was guided by targeting LDL-C between 0.6-1.3mmol/L.

BACKGROUND

- Patients who have experienced an ACS remain at high risk of recurrent ischemic events despite receiving standard high-intensity statin therapy which has already been proven to lower this risk.[2,3,4]
- PCSK9 inhibitors like alirocumab lower LDL cholesterol levels primarily by increasing the number of LDL receptors available to clear LDL from the bloodstream.[7]
- **FOURIER** Trial (2017): studied the PCSK9 inhibitor evolocumab in patients with established cardiovascular disease (CVD) and found that it significantly reduced LDL cholesterol and, more importantly, the risk of cardiovascular events.[6]

STUDY BACKGROUND

DESIGN: Multicenter (1315 sites in 57 countries), randomized, double-blind, allocation concealed, placebo-controlled trial.

INTERVENTION: Alirocumab PRALUENT 75mg subcutaneous every two weeks, with dose adjustments to target LDL cholesterol between 0.6-1.3mmol/L vs matching placebo injection very two weeks.

INCLUSION: Age >40, history of ACS (myocardial infarction of unstable angina within 1-12 months. LDL cholesterol level ≥1.8mmol/L, or non-HDL cholesterol ≥2.6mmol/L, or apolipoprotein B ≥ 4.44mmol/L; all measured after at least two weeks of stable high-intensity statin therapy (**atorvastatin 40–80mg daily** or **rosuvastatin 20–40mg daily**) or the maximum tolerated dose of one of these statins (including no statin in the case of documented unacceptable side effects).

EXCLUSION: LDL cholesterol <1.8mmol/L after high-intensity statin use, ACS event <1 month or >12 months prior, severe uncontrolled hypertension, NYHA class III or IV heart failure, severe renal impairment, significant liver disease (ALT/AST >3x ULN), recent cancer (within 5 years), known hypersensitivity to alirocumab, pregnant or breastfeeding women, participants in other clinical trials within 30 days, and those with a life expectancy of less than three years.

POPULATION at baseline: n= 18,924 enrolled; mean age 59 yrs, 75% male, 80% White, 13% Asian, 3% Black.

- Clinical presentation (index ACS): 83% MI, 17% unstable angina; 2.6 months median time from ACS to randomization.
- Medical History before index ACS: 65% HTN, 29% DM, 24% tobacco smoker, 36% family history of premature CHD, 19% MI, 17% PCI, 15% CHF, 6% CABG, 3% stroke, 4% PAD.
- Mean population LDL-C at baseline approximately 2.38 mmol/L.

Clinical Endpoints	Alirocumab n=9462 (randomized)	Placebo n =9462 (randomized)	ARR/ARI (%) Hazard Ratio	NNT/NNH /2.8 yrs	Comments
PRIMARY ENDPOINT (Composite) - (ITT data from Table 2)					**Primary and Secondary Outcomes:** **Primary Endpoint Kaplan-Meier Estimate NNT @ 4 years = 49** **Death from any cause:** modest but considered clinically significant, favorable and reassuring **Safety/AEs/Other/Subgroups:** **Injection Site Reactions:** Generally mild and manageable. Led to discontinuation in 26 participants of the Alirocumab arm vs 3 in the placebo arm. **Higher Baseline LDL-C Patients:** Greater absolute benefit **(↓3.4% ARR in primary endpoint**) seen in patients with LDL cholesterol levels ≥2.6mmol/L (and therefore subsequently higher dosed therapy). Supports targeting PCSK9 inhibitors for patients with significantly elevated LDL levels despite statin therapy.
CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization	903 (9.5)	1052 (11.1)	↓1.6% p<0.001 0.85 (0.78-0.93)	**63 (56-70 95% CI)**	
SECONDARY ENDPOINTS, in order of hierarchical testing:					
Any coronary heart disease event	1199 (12.7)	1349 (14.3)	↓1.6% 0.88 (0.81–0.95)	**63**	
Major coronary heart disease event	793 (8.4)	899 (9.5)	↓1.1% 0.88 (0.80–0.96)	**91**	
Any cardiovascular event	1301 (13.7)	1474 (15.6)	↓1.9% 0.87 (0.81–0.94)	**52**	
Composite of primary endpoint**, death from any cause §	973 (10.3)	1126 (11.9)	↓1.6% 0.86 (0.79–0.93)	**63**	
Death from coronary heart disease	205 (2.2)	222 (2.3)	↓0.1% 0.92 (0.76–1.11) *		
Death from cardiovascular causes	240 (2.5)	271 (2.9)	↓0.4% 0.88 (0.74–1.05) *		
Death from any cause	334 (3.5)	392 (4.1)	↓0.6% 0.85 (0.73-0.98) *		

CLINICAL ENDPOINTS	ALIROCUMAB n=9462 (randomized)	PLACEBO n =9462 (randomized)	ARR/ARI (%) HAZARD RATIO	NNT/NNH /2.8 yrs	COMMENTS
Safety/Other Endpoints‖:					**Diabetes risk:** Diabetes worsening or related complications and new onset diabetes were lower in alirocumab arm (18.8%, 9.6%) vs placebo (21.2%, 10.1%) respectively, indicating a favorable comorbid diabetes profile.
Nonfatal myocardial infarction	626 (6.6)	722 (7.6)	↓1.1% 0.86 (0.77–0.96)		
Fatal or nonfatal ischemic stroke	111 (1.2)	152 (1.6)	↓0.4% 0.73 (0.57–0.93)		
Unstable angina requiring hospitalization	37 (0.4)	60 (0.6)	↓0.2% 0.61 (0.41–0.92)		
Ischemia-driven coronary revascularization procedure	731 (7.7)	828 (8.8)	↓1.1% 0.88 (0.79–0.97)		
Hospitalization for CHF	176 (1.9)	179 (1.9)	No difference		
Serious Adverse Events	2202 (23.3)	2350 (24.9)	↓1.6%	63	
Discontinuation Rates	1343 (14.2)	1496 (15.8)	↓1.6%	NS	
Injection Site Reactions	360 (3.8)	203 (2.1)	↑1.7%	60	

***** The hierarchical analysis was stopped after the first nonsignificant P value was observed, in accordance with the hierarchical testing plan therefore no NNT's subsequent were calculated.
****** Composite of primary endpoint includes nonfatal myocardial infarction, and nonfatal ischemic stroke
§ The widths of the confidence intervals for the secondary end points were not adjusted for multiplicity, so the intervals for the outcomes listed below this outcome should not be used to infer definitive treatment effects
‖ The analysis for other end points was not adjusted for multiplicity; therefore, no P values or NNT's reported.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Large sample size (18,924 patients), robust design with double-blind, placebo-controlled methodology, and inclusion of high-risk post-ACS patients, providing strong evidence for alirocumab's efficacy and safety profile. Randomization and blinding were well-maintained, minimizing bias.
- Interim analysis performed at 50% and 75% of the planned primary end point events for final analysis. Neither indicated cause for early termination. Two-sided P-value of less than 0.0498 was used to declare statistical significance to compensate for interim analysis procedures.
- ITT strength in superiority trial – maintains prognostic balance.
- Other medications at randomization were similar between groups.
- **ODYSSEY** Open-Label Extension (**OLE**) study, published in 2018 in *Atherosclerosis*, investigated the long-term efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia (HeFH). The mean LDL-C reduction was approximately 50% from baseline, which was maintained throughout the study duration. In total, 985 patients with HeFH received alirocumab (median duration 2.5 years). No new safety concerns emerged during the extended treatment period. Rates of adverse events did not increase over time, suggesting a consistent safety profile with long-term use.[5]

LIMITATIONS:

- The trial primarily involved patients already on high-intensity statins, or at the maximum tolerated dose. The exclusion of patients with lower LDL-C levels or those not on high-intensity statins might limit broader applicability.
- Recent ACS within the last 1-12 months may limit applicability.

UNCERTAINTIES:

- The trial allowed for the use of other lipid-lowering therapies, such as ezetimibe, alongside maximally tolerated statins. How might the influence of differing combination therapies alter the results?
- How does PCSK9 inhibition, as examined in the **ODYSSEY** trial with a focus on LDL-C reduction and cardiovascular outcomes, impact non-LDL-related pathways such as inflammation or plaque stability, and what further research is needed to clarify these effects?
- Treat-to-target approach used but would fire-and-forget give similar results? Would we need to be cautious in patients that do not have exceptionally high LDL-C values? Further examination of PCSK9i comparing clinical endpoint outcomes of treatment approaches may be warranted.
- Industry involvement in design and implementation of the trial raises potential for bias; the Kaplan-Meier NNT estimate at 4 years, instead of the median 2.8 might be an example of "favourable reporting".
- Would patients who experienced an ACS past 12 months see similar benefit?

Other notes of interest:

Cost: Alirocumab 75mg subcutaneously every 2 weeks ~$570 CAN per month (Saskatchewan EDS and NIHB prior approval criteria for coverage).

- Cost effectiveness analysis based on the population of the very similar **FOURIER** trial, PCSK9i intervention produced a negative return on investment of 86% for private payers.[8] The investigators noted the price of PCSK9i would need to drop 62%, to $5459 USD per year, to reach $100 000 USD per quality-adjusted life year which is the commonly accepted societal threshold. [8]

ACS=acute coronary syndrome **AE**=adverse event **ALT**=alanine transaminase **ARI**=absolute risk increase **ARR**=absolute risk reduction **AST**=aspartate aminotransferase **CABG**=coronary artery bypass grafting **CAD**=Canadian dollar **CHD**=coronary heart disease **CHF**=congestive heart failure **CV**=cardiovascular **CVD**=cardiovascular disease **DM**=diabetes **HDL**=high-density lipoprotein **HeFH**=heterozygous familial hypercholesterolemia **HTN**=hypertension **ITT**=intention-to-treat analysis **L**=litre **LDL**=low-density lipoprotein **mg**=milligram **MI**=myocardial infarction **mmol**=millimole **n**=number **NIHB**=non-insured health benefits **NNT**=number needed to treat **NNH**=number needed to harm NS=non-significant **NYHA**=New York Heart Association **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention **PCSK9i**=proprotein convertase subtilisin/kexin type 9 inhibitor **ULN**=upper limit of normal **USD**=United States dollar **yr**=year

RxFILES RELATED LINKS

- **Landmark Lipid Trials**: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf
- **Lipid Lowering Therapy – Drug Comparison Chart**: https://www.rxfiles.ca/RxFiles/uploads/documents/members/CHT-lipid%20agents.pdf

ACKNOWLEDGEMENTS: **Prepared By**: Nicholas Trischuk **Contributors**: Loren Regier **Reviewers**: Taisa Trischuk
DISCLOSURES: No conflicts of interest to disclose.

References:

1. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018 Nov 29;379(22):2097-2107.
2. Canadian Cardiovascular Society. (2021). *2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults*. Canadian Journal of Cardiology, 37(9), 1129-1150. https://doi.org/10.1016/j.cjca.2021.03.016
3. Arora, P., Singh, A., & Anker, S. D. (2023). Real-world risk of recurrent cardiovascular events in atherosclerotic cardiovascular disease patients with LDL-C above guideline-recommended threshold: A retrospective observational study. *Cardiology and Therapy*, 12(1), 123-135. https://doi.org/10.1007/s40119-022-00278-6
4. European Society of Cardiology. (2023). *2023 ESC guidelines for the management of acute coronary syndromes*. https://www.escardio.org/guidelines
5. Kastelein, J. J. P., Ginsberg, H. N., Langslet, G., Hovingh, G. K., Ceska, R., Dufour, R., ... & Stein, E. A. (2018). ODYSSEY FH I and FH II: 78-week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Atherosclerosis*, 277, 293-297. https://doi.org/10.1016/j.atherosclerosis.2018.06.003
6. Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., ... & Wasserman, S. M. (2017). Evolocumab and clinical outcomes in patients with cardiovascular disease. New England Journal of Medicine, 376(18), 1713-1722. https://doi.org/10.1056/NEJMoa1615664
7. Toth, P. P., et al. (2020). PCSK9 inhibitors: Mechanism of action, efficacy, and safety. Nature Reviews Cardiology, 17(1), 30-42. https://doi.org/10.1038/s41569-019-0242-2
8. Arrieta, A., Hong, J. C., Khera, R., Virani, S. S., Krumholz, H. M., & Nasir, K. (2017). Updated cost-effectiveness assessments of PCSK9 inhibitors from the perspectives of the health system and private payers: Insights derived from the FOURIER trial. *JAMA Cardiology, 2*(12), 1369-1374. https://doi.org/10.1001/jamacardio.2017.3655:contentReference[oaicite:0]{index=0}.