EE682

Kirk Szafranski | kirk.szafranski@eversana.com

Targeted Literature Review Informing Economic Model Structures in Atherosclerotic Cardiovascular Disease

Luiz Causin, MS[1], Kirk Szafranski, MSc[2], Maria Caiado, MASc[1], Sandra Vigelis, MBiotech[2], Juliette Neyra, PharmD[3], Pamela Vo, MS, PharmD[4].
[1]Novartis Pharmaceuticals UK Ltd, London, United Kingdom, [2]EVERSANA, Burlington, ON, Canada, [3]Novartis Pharmaceuticals Canada Inc, Montreal, QC, Canada, [4]EVERSANA, Basel, Switzerland.

This study was sponsored by Novartis. L. Causin, M. Caiado, and J. Neyra are employees of Novartis. K. Szafranski, S. Vigelis, and P. Vo are employees of EVERSANA. EVERSANA receives consultancy fees from pharmaceutical and device companies, including Novartis.
Poster presented at the Professional Society for Health Economics and Outcomes Research (ISPOR) Europe 2025 (9-12 November) at Glasgow, Scotland, UK.

KEY FINDINGS & CONCLUSIONS

- A total of 83 records were included in this literature review, of which 56 records were selected for data extraction and analysis.
- Markov cohort models were the predominant model structure in both HTA submissions (89%) and journal articles (85%) in ASCVD.
- Although the choice of model structure used in HTA submissions in ASCVD tends to follow the precedence of previous ASCVD submissions (ie, Markov cohort), other types of model structures are also feasible and can be accepted by HTA agencies. In contrast, a greater diversity of model structures in ASCVD is present in published journal articles.
- Ultimately, the choice of model structure depends on the specific decision problem and limitations of the data source.

INTRODUCTION

- Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality worldwide, affecting more than 380 million people.[1,2] As of 2015, cardiovascular (CV) disease accounted for approximately one-third of all deaths globally, with 85% resulting from myocardial infarction or stroke.[2]
- Both a chronic and progressive disease, ASCVD is characterized by the accumulation of lipids and fibrous material within the arteries, resulting in the formation of atherosclerotic plaques.[3] These plaque formations can ultimately lead to CV events, such as stroke.[3,4] A major causal factor of ASCVD is elevated lipid levels, such as low-density lipoprotein cholesterol (LDL-C).[5]
- The current standard of care for ASCVD consists of lipid-lowering therapies, including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is); however, despite treatment, LDL-C levels often remain high, with only <30% of patients with ASCVD achieving guideline-recommended reductions in LDL-C.[6]

OBJECTIVE

- To conduct a targeted literature review (TLR) to identify, characterize, and critically appraise published cost-effectiveness models (CEMs) in ASCVD from key health technology assessment (HTA) agencies and journal articles.

METHODS

- A TLR was performed in October 2024 using HTA agency websites and a MEDLINE database search (**Figure 1**).
- Pre-defined population, intervention/comparators, outcomes, and study type (PICOS) criteria (**Table 1**) were employed to screen identified records during the title/abstract (first pass) and full text (second pass) screening.

Figure 1. Overview of Methods used in the Targeted Literature Review

1. Targeted search of:
   1. HTA websites:
      - NICE (UK)
      - CDA-AMC (Canada)
      - PBAC (Australia)
      - ICER (US)
   2. MEDLINE via Ovid
2. Screening of HTA submissions and journal articles publications eligible for inclusion based on PICOS criteria
3. Search of the CEVR to ensure all relevant models were captured
4. Extraction of key model details, assumptions, and limitations/ criticisms from included studies in a standardized table
5. Identifying and summarizing the key findings/insights, along with a critical evaluation of published models

Abbreviations: CDA-AMC = Canada's Drug Agency; CEVR = Center for the Evaluation of Value and Risk; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PICOS = population, intervention/comparators, outcomes, and study type; UK = United Kingdom; US = United States.

Table 1. PICOS Inclusion Criteria

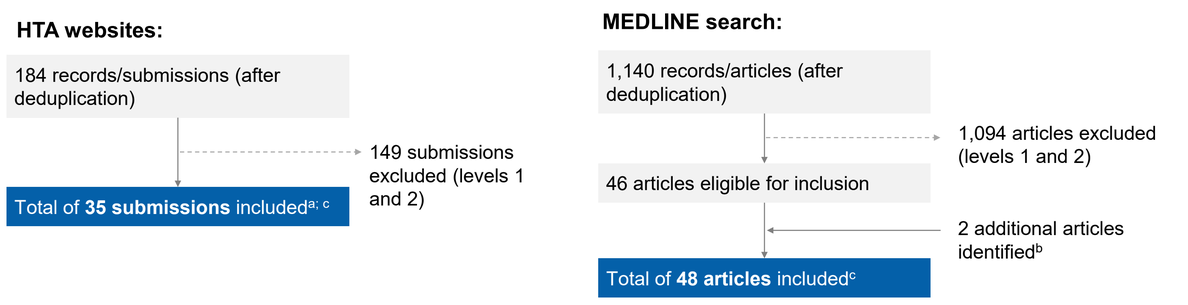
Category	Inclusion Criteria
Population	• Adults with ASCVD
Intervention/ Comparators	• Any drug therapy
Outcomes	• Summary cost outcomes including total costs and costs for different health states • Summary health outcomes including life years and quality-adjusted life years • Incremental cost-effectiveness ratio
Study type	• CEA or CUA that models MACE or its components as a key outcome[a]
Location	• Global
Language	• English

[a] Although reviews were not included in the literature review, any included reviews were searched for relevant CEAs/CUAs.
Note: a date limit of 2021 was selected to allow for the capture of the most recent CEAs/CUAs for lipid-lowering therapies. However, as PCSK9is are a key treatment in ASCVD, any HTA submissions with PCSK9is submitted/published prior 2021 were also included in the literature review.
Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; HTA = health technology assessment; MACE = major adverse cardiovascular event; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; PICOS = population, intervention/comparators, outcomes, and study type.

RESULTS

- A total of 35 and 48 records were identified via HTA websites and the MEDLINE search, respectively (**Figure 2**).

Figure 2. Records Identified via HTA Websites and the MEDLINE Search

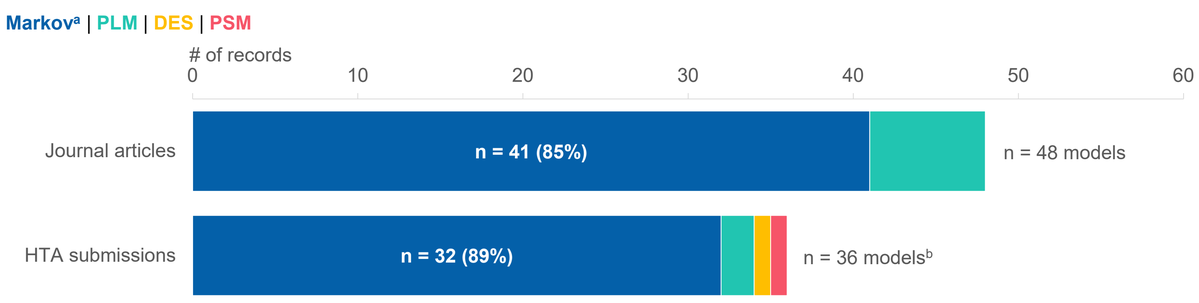


[a] Includes both initial and resubmissions to HTA agencies. [b] Identified through hand searching economic literature reviews and supplemental search of the CEVR CEA registry. [c] All included submissions (35 submissions) were extracted and analysed, whereas a subset of all included articles (21 articles), were selected for data extraction and analysis.
Abbreviations: CEA = cost-effectiveness analysis; CEVR = Center for the Evaluation of Value and Risk; HTA = health technology assessment.

Detailed Breakdowns of Included/Extracted Models

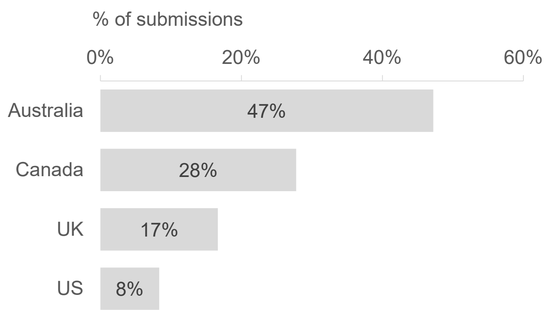
- The majority of models were Markov cohort in both HTA submissions (89%) and journal articles (85%; **Figure 3**).
- Nearly half of the HTA submissions were from Australia (47%), followed by Canada (28%), the United Kingdom (UK; 17%), and the United States (US; 8%; **Figure 4**). In terms of journal articles, the highest proportion were from China (26%), followed by the US (17%), and various other countries (**Figure 5**).

Figure 3. Breakdown of Model Structures from Included HTA Submissions and Articles



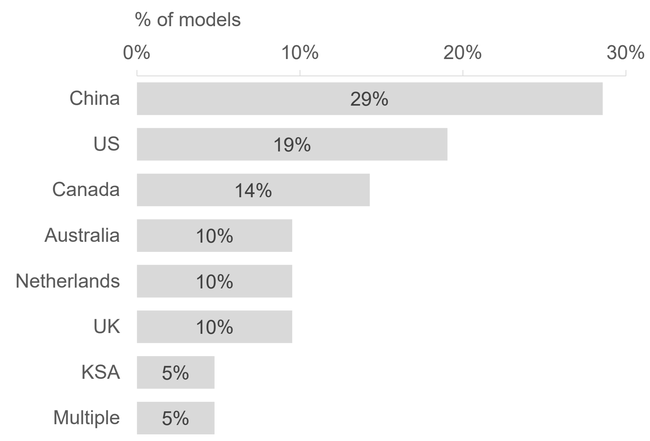
[a] Refers to Markov cohort. [b] One submission (ticagrelor submitted to CDA-AMC) included both a Markov cohort and a PLM,[7] which are counted as two separate models.
Abbreviations: CDA-AMC = Canada's Drug Agency; DES = discrete-event simulation; HTA = health technology assessment; PLM = patient-level simulation model; PSM = partitioned-survival model.

Figure 4. Breakdown of Countries from Extracted HTA Submissions (n = 35)



Abbreviations: HTA = health technology assessment; UK = United Kingdom; US = United States.

Figure 5. Breakdown of Countries from Extracted Articles (n = 21[a])



[a] A subset of all included articles were selected for data extraction and analysis.
Note: "Multiple" consisted of an article that assessed Canada, France, and Germany (n = 1).
Abbreviations: KSA = Kingdom of Saudi Arabia; UK = United Kingdom; US = United States.

Key Takeaways from HTA Submissions and Articles

- Across HTA submissions, a common criticism from the NICE and CDA-AMC was the use of LDL-C as a surrogate for CV events; notably, PBAC and ICER reports suggested that a patient-level approach could be an alternative approach compared to a cohort model (**Figure 6**).
- In terms of journal articles, models linked to HTA submissions tended to assess more specific populations within ASCVD; published patient-level simulations (PLMs) in ASCVD demonstrate that different models have been developed for manuscript publication versus HTA submission (**Figure 7**).

Figure 6. Key Takeaways from Extracted HTA Submissions

NICE (UK)
- A common criticism across models was the use of LDL-C as a surrogate for CV events.[9-14]
- The use of a composite outcome (ie, MACE) was criticized, and thus, may be less preferable than modelling events individually.[10]
- There were concerns over health states in the evolocumab model (Markov), which had **13 composite states based on arbitrary assumptions** (not data).[11]

CDA-AMC (Canada)
- Similar to NICE, a common criticism across models was the use of LDL-C as a surrogate for CV events.[15-18]
- The sponsor for ticagrelor originally submitted a **PLM**; however, upon CDA-AMC's request, the sponsor for ticagrelor had later provided a Markov model.[7]

PBAC (Australia)
- PBAC stated that a **microsimulation approach (instead of a Markov cohort) may have been more appropriate** for rivaroxaban, as it has a greater ability to track events over time and given the baseline heterogeneity; **rivaroxaban was resubmitted with a DES model, which ultimately received a positive recommendation**.[19-21]

ICER (US)
- Public comment on the rivaroxaban/icosapent ethyl model **suggested to conduct a PLM**; however, ICER responded that they did not have access to patient-level data, and that ultimately, a PLM would not lead to differences in average incremental results.[22]

Abbreviations: CDA-AMC = Canada's Drug Agency; CV = cardiovascular; DES = discrete-event simulation; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PLM = patient-level simulation model; UK = United Kingdom; US = United States.

Figure 7. Key Takeaways from Extracted Articles

Models linked to HTA submissions (n = 10[a])
- Of the drugs with linked models, all consisted of 1 to 2 linked journal article(s), except for **evolocumab**, which consisted of **7 linked journal articles**.[23-29]
- Linked models between HTA submissions and journal articles (for the same drug) were **overall similar**; the most commonly noted difference across several ASCVD drugs was assessing different subgroups, with **journal articles tending to assess more specific/narrower populations** (eg, patients with CAD, prior MI, and renal impairment).[27-30]

Unlinked Markov cohort models (n = 4)
- All models consisted of **3 to 6 health states**, including MI as a key CV event.[31-34]
- Authors stated that **treatment adherence** (ie, not assuming 100%), as well as conducting **key subgroup analyses** (eg, specific LDL-C thresholds, different racial/ethnic populations) **should be considered**.[33-34]

Unlinked PLMs (n = 7)
- There were only 4 separate/different models, as **several publications were based on the same model** (with only small differences in the perspectives or patient population).
- 4 PLMs assessed treatments that were submitted to HTA agencies with a Markov cohort structure (2 assessing icosapent ethyl ± statins,[30,35] 2 assessing rivaroxaban + ASA),[8,36] demonstrating that **drugs in ASCVD** have developed **different models for publication versus HTA submission**.

[a] Linked to 23 included HTA submissions.
Abbreviations: ASA = acetylsalicylic acid; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CV = cardiovascular; HTA = health technology assessment; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PLM = patient-level simulation model;

Critical Evaluation of Models Submitted to HTA Agencies

- Across the included models, efficacy was typically informed using a surrogate outcome (ie, reductions in LDL-C linked to CV event risk); this was a common criticism across HTA agencies, as the use of a surrogate outcome is linked to uncertainty within economic models.[7,9-14,15-18]
- Notably, icosapent ethyl submissions in ASCVD across HTA agencies used various model structures (ie, partitioned-survival to NICE, with Markov cohort and a PLM as additional validation models;[15] Markov cohort to both CDA-AMC[37] and PBAC[38,39]). Ultimately, positive recommendations were issued from these HTA agencies.
- Further, one submission to CDA-AMC (for ticagrelor in ASCVD) initially submitted a PLM, however, upon CDA-AMC's request, the sponsor submitted Markov model.[7]

Acknowledgements

The authors acknowledge **Rachid Rafia** (Novartis), as well as **Chris Drudge**, **Alexandra Hall**, **Sofiya Portuhay**, and **Allen Zhou** (EVERSANA), for supporting content development.

The final responsibility for the content lies with the authors.

References

1. Barquera S. Arch Med Res. 2015;46(5):328-338.
2. Roth GA. J Am Coll Cardiol. 2020;76(25):2982-3021.
3. Libby P. Nat Rev Dis Primers. 2019;5(1):56.
4. Jebari-Benslaiman S. Int J Mol Sci. 2022;23(6):3346.
5. Ference BA. Eur Heart J. 2017;38(32):2459-2472.
6. Underberg J. Postgrad Med. 2022;134(8):752-762.
7. CDA-AMC (2016). Ticagrelor. SR0474-000.
8. Lamy A. Eur Heart J Qual Care Clin Outcomes. 2023;9(5):502-510.
9. NICE (2021). Bempedoic acid with ezetimibe. TA694.
10. NICE (2016). Alirocumab. TA393.
11. NICE (2016). Evolocumab TA394.
12. NICE (2021). Inclisiran. TA733.
13. NICE (2016). Ezetimibe. TA385.
14. NICE (2022). Icosapent ethyl with statin therapy. TA805.
15. CDA-AMC (2022). Inclisiran. SR0681-000.
16. CDA-AMC (2016). Evolocumab. SR0441-000.
17. CDA-AMC (2017). Evolocumab. SR0515-000.
18. CDA-AMC (2024). Evolocumab. SR0821-000.
19. PBAC (2019). RIVAROXABAN. March 2019.
20. PBAC (2020). RIVAROXABAN. March 2020.
21. PBAC (2020). RIVAROXABAN. July 2020.
22. ICER (2019) CVD: Additive Therapies. August 2019.
23. Alghamdi A. Pharmacoecon Open. 2022;6(2):277-291.
24. Gregoire J. Adv Ther. 2022;39(7):3262-3279.
25. Kotsopoulos N. J Med Econ. 2021;24(1):123-130.
26. Liang Z. Cardiovasc Drugs Ther. 2021; 35(4):775-785.
27. Wan Y. Cost Eff Resour Alloc. 2023;21(1):93.
28. Xie W. Adv Ther. 2023;40(2):489-503.
29. Xi X. Cardiovasc Drugs Ther. 2023;37(5):905-916.
30. Weintraub WS. JAMA Netw Open. 2022;5(2):e2148172.
31. Burvill A. J Clin Lipidol. 2024;18(6):e946-e956.
32. Liang Z. Front Pharmacol. 2021;12:648244.
33. Boczar KE. CJC Open. 2022;4(5):441-448.
34. Zhou W. Front Pharmacol. 2024;15:1283922.
35. Weintraub WS. J Am Heart Assoc. 2024;13(1):e032413.
36. Lamy A. Am J Cardiovasc Drugs. 2024;24(1):117-127.
37. CDA-AMC (2020) Icosapent ethyl. SR0619-000.
38. PBAC (2023) ICOSAPENT ETHYL. November 2023.
39. PBAC (2024) ICOSAPENT ETHYL. March 2024.

Scan to obtain:
- Poster