

Modelling Methods for Economic Evaluations of Non-Statin Lipid Lowering Therapies for Reducing Cardiovascular Risk: A Systematic Literature Review

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Jawla S, MPharm¹; Gaba U, MPH²; Gupta R, MPH²; Radotra A, MPH²

¹Daiichi Sankyo Europe GmbH, Munich, Germany; ²Skyward Analytics, Gurugram, Haryana, India

INTRODUCTION

- Cardiovascular (CV) diseases are a leading cause of mortality worldwide.¹ While statin therapies are the first-line standard for cholesterol management leading to CV risk reduction, many patients are not able to reach their cholesterol goals or tolerate statin-related adverse effects^{2,3}
- As the number of lipid-lowering therapies (LLTs) continues to grow, it becomes increasingly important for stakeholders and payers involved in lipid management to understand how the cost-effectiveness of these therapies is assessed
- This systematic literature review (SLR) aimed to summarize and assess the quality of published economic evaluations conducted across Europe on LLTs in individuals at high CV risk or those with established CV disease

METHODS

- Searches were conducted in Embase, Medline, and the Cochrane Library (via OVID), as well as Google Scholar, up to February 08, 2023, in accordance with the Cochrane guidelines
- Studies were included if they assessed adults with CV disease or at high CV risk, receiving maximally tolerated statins (with or without LLTs or placebo), or statin-intolerant patients treated with bempedoic acid, alirocumab, evolocumab, ezetimibe, or inclisiran—either as monotherapy or in combination with statins or ezetimibe
- The quality of included studies was assessed using the 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

RESULTS

- Seventeen studies were identified (**Figure 1**), primarily conducted from a healthcare-payer perspective across Europe (**Table 1**). Markov models were the most commonly employed, majority of the outcomes were modelled for a lifetime horizon, and varying discount rates (3-5.5%)
- Modelled outcomes included events averted, quality-adjusted life years (QALY) gained, life years (LY) gained, incremental costs and incremental cost-effectiveness ratios (ICER)
- Included studies evaluated the cost-effectiveness of alirocumab, evolocumab, ezetimibe, bempedoic acid, and inclisiran, with varying outcomes and conclusions reported across studies (**Table 2**)
- Quality assessment using the CHEERS checklist indicated that the quality of studies varied, with a median score of 76% (**Table 3**)

Figure 1. PRISMA flow diagram depicting study selection and inclusion process

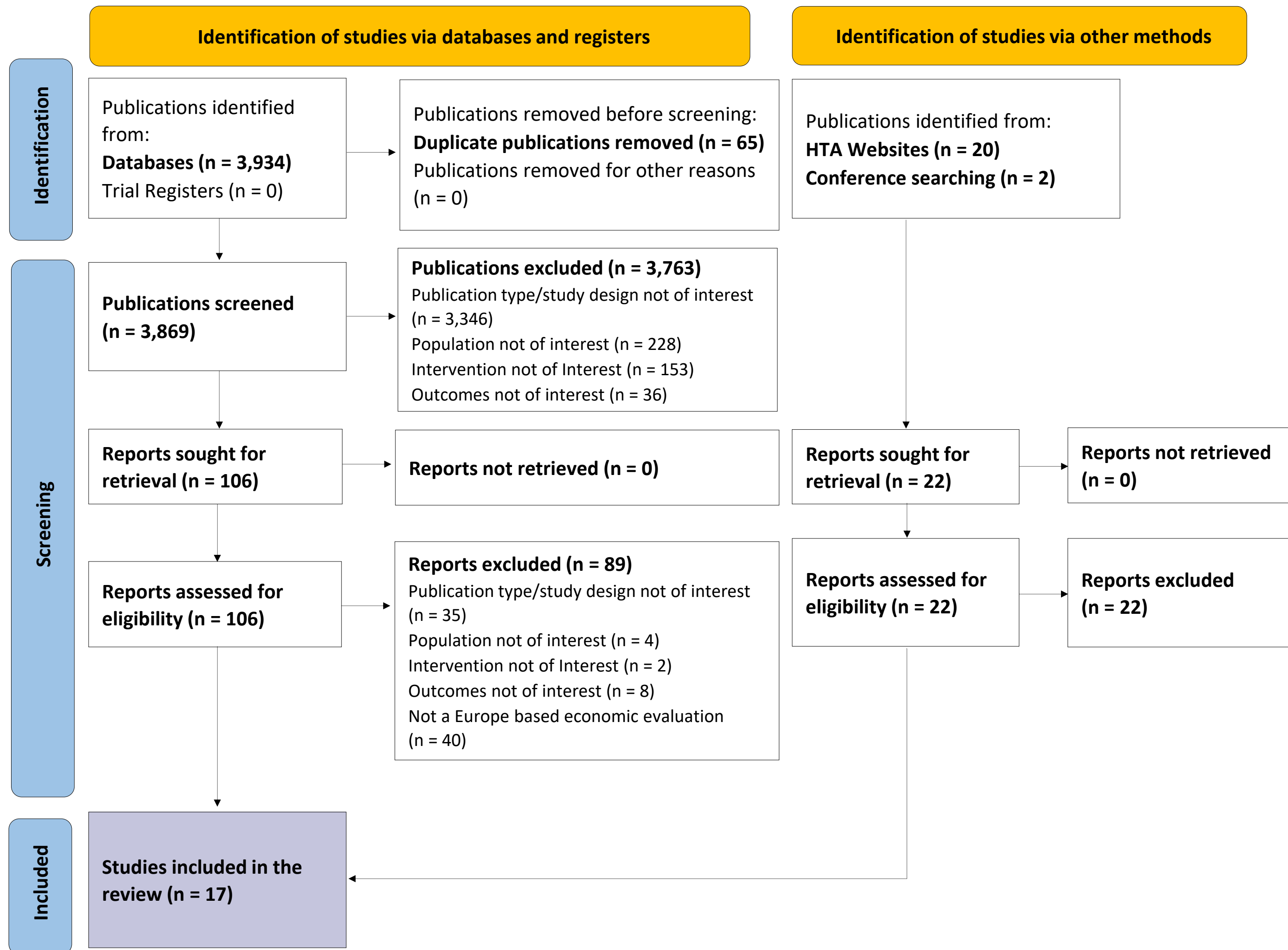


Table 1. Summary of the economic evaluation studies

Author	Country; WTP considered	Time Horizon	Cycle length	Perspective	Discount rate	Intervention	Comparator	Currency; Costing year
Seijas-Amigo et al., 2023 ⁴	Spain; €20,000/QALY	Five years	NR	Societal	5.5%	PCSK9 Inhibitors + statin	Bempedoic acid + statin	Euros; 2021
Galactionova et al., 2022 ⁵	Switzerland; CHF 30,000/QALY	Lifetime	1 year	Payer	3.0%	Inclisiran + SOC	SOC	CHF; 2018
Michaeli et al., 2022a ⁶	UK; £20,000 to £30,000/QALY	20 years (lifetime)	NR	Payer	3.5%	Ezetimibe + statin, Evolocumab + statin, Alirocumab + statin	Statin monotherapy	Pounds; 2021
Michaeli et al., 2022b ⁷	Germany; €20,000/QALY	20 years (lifetime)	NR	Payer	3.0%	Ezetimibe + statin, Evolocumab + statin, Alirocumab + statin	Statin monotherapy	Euros; 2021
Povero et al., 2020 ⁸	Italy; €30,000/LY	Lifetime	1 year	Payer	NR	Alirocumab + maximum dose tolerated statin plus Ezetimibe (MDTS + ezetimibe)	MDTS + ezetimibe	Euros; NR
Korman et al., 2018 ⁹	Norway; 600,000 NOK/QALY	Lifetime	1 year	NR	4.0%	Evolocumab + alirocumab	Ezetimibe + standard treatment	Euros; 2015
Olry de Labry Lima A et al., 2018 ¹⁰	Spain; NR	26 months (Decision tree) and 10 years (Markov model)	NR (Decision tree); 1 month (Markov model)	Payer	NR	Evolocumab + statins	Standard therapy (statins and statins + ezetimibe)	Euros; 2017
Stam-Slob et al., 2018 ¹¹	Netherlands; Up to €100,000/QALY	Lifetime	1 year	Payer	3.0%	PCSK9 inhibitors + standard LLT	Standard LLT	Euros; 2014
Villa et al., 2017 ¹²	Spain; €45,000/QALY	Lifetime	1 year	Payer	3.0%	Evolocumab + SOC	SOC	Euros; 2016
Laires et al., 2015 ¹³	Portugal; €30,000/QALY	Lifetime (up to the age of 100 years)	1 year	Payer	5.0%	Rosuvastatin or Atorvastatin + ezetimibe	Atorvastatin	Euros; 2015
Nooten et al., 2011 ¹⁴	Netherlands; €20,000 to €40,000/QALY	Lifetime	1 year	Societal	4% for costs and 1.5% for outcomes	Ezetimibe + simvastatin therapy	Statin monotherapy	Euros; NR
Reckless et al., 2010 ¹⁵	UK; NR	Lifetime	1 year	Payer	3.5%	Ezetimibe/Simvastatin	LDL-lowering potencies [#]	Pounds; 2004
Soini et al., 2010 ¹⁶	Finland	Lifetime	1 year	Societal	3% for costs and QALYs	Simvastatin	Atorvastatin, rosuvastatin, ezetimibe + simvastatin	Euros; 2007
Ara et al., 2008a ¹⁷	UK; £30,000/QALY	Lifetime	1 year	Payer	3.5%	Ezetimibe monotherapy	No treatment	Pounds; 2006
Ara et al., 2008b ¹⁸	UK; £30,000/QALY	Lifetime	1 year	Payer	3.5%	Ezetimibe + statin therapy	Statin monotherapy (simvastatin/ atorvastatin)	Pounds; 2006
Cook et al., 2004 ¹⁹	Germany, Spain, and Norway; NR	Lifetime	1 year	Payer	3.0%	Ezetimibe + statin (atorvastatin + simvastatin)	Atorvastatin titration + simvastatin titration	Euros; 2004
Landmesser et al., 2022 ²⁰	Sweden; SEK700,000/QALY	Lifetime	1 year	NR	3.0%	Evolocumab + SOC	SOC	SEK; 2019

[#]LDL-lowering potencies: a) Low-potency: Fluvastatin, Pravastatin, Simvastatin; b) Medium-potency: Atorvastatin, Simvastatin; c) Higher potency: Atorvastatin, Rosuvastatin, Simvastatin.
Abbreviations: CHF, Swiss Franc; LDL, Low density lipoprotein; LY, Life years gained; MDTS, Maximum dose tolerated statin; NR, not reported; QALY, Quality adjusted life years; SOC, Standard of care; UK, United Kingdom; WTP, Willingness to Pay.

- In total, 16 of the 17 publications were included in the quality assessment using the 2022 CHEERS checklist. Quality assessment for Povero et al., 2020 could not be done as only the abstract was published without any associated poster/slides, limiting the information available
- The quality of reporting ranged from 54% to 86%, with a median of 76%
- Most articles discussed the methods for measuring and validating costs (n = 15) and the impact of uncertainty on the outcomes (n = 16)

Table 2. Characteristics of included economic evaluations

Characteristic	Category	Number of studies	Sources
Publication Year	2004 to 2013	6	[14-19]
	2014 to 2023	11	[4-13, 20]
Economic evaluation	Cost-effectiveness analysis	17	[4-20]
Type of model	Markov model	15	[5-9, 11-20]
	Markov and decision tree	1	[10]
	NR	1	[4]
Time Horizon (Years)	Lifetime	14	[5, 6, 8, 9, 11-20]
	5 years	1	[4]
	20 years	1	[7]
	26 months and 10 years	1*	[10]
Study Perspective	Healthcare payer	12	[5-8, 10-13, 15, 17-19]
	Societal perspective	3	[4, 14, 16]
	NR	2	[9, 20]
Discount Rate (%)	3.0%^	7	[5, 7, 11, 12, 16, 19, 20]
	3.5%	3	[6, 15, 17]
	4.0%	1	[9]
	4% costs and 1.5% outcomes	1	[14]
	5.0%	1	[4]
	5.5%	1	[13]
	NR	1	[8]
	No discounting	1*	[10]
Countries	United Kingdom	4	[6, 15, 17, 18]
	Spain	3	[4 10, 12]
	Netherlands	2	[11, 14]
	Finland	1	[16]
	Germany	1	[7]
	Germany, Spain, and Norway	1	[19]
	Italy	1	[8]
	Norway	1	[9]
	Portugal	1	[13]
	Sweden	1	[20]
	Switzerland	1	[5]

*In their economic evaluation, de Labry Lima et al., 2018 utilized both a decision tree and a Markov model, with a time horizon of 26 months for the decision tree and 10 years for the Markov model. No discount rate was employed in the Markov model [10]
^Among the studies with 3% discount rate, in one study LYs gained were not discounted [12]

- The least addressed criteria were characterizing distributional effects, characterizing heterogeneity, approach to engaging with patients and other affected stakeholders in the study and assessing the impact of this involvement
- Characterization of heterogeneity was described in only two studies^{5,13}
- Distributional effects were only reported in only two studies^{5,12}
- None of the included studies reported the impact of engaging with patients and other affected stakeholders

Table 3. Quality assessment using CHEERS checklist

Quality Rating	Criterion %	Sources
Excellent	≥85%	[13]
Very Good	≥70%-84%	[5-7, 9, 12, 14, 15-18]
Good	55%-70%	[10, 11, 19, 20]
Poor	<55%	[4]

Abbreviations: CHEERS, Consolidated Health Economic Evaluation Reporting Standards.

CONCLUSIONS

- This SLR summarizes 17 economic evaluations assessing the cost-effectiveness of non-statin LLTs for managing CV disease and CV risk in European countries, providing valuable insights to health economists and researchers in the field of CV health
- The economic models primarily utilized Markov cohort models, demonstrating consistency in structure despite variations in health states
- The reporting quality in most studies was 'very good', reflecting robust methodologies and suggesting that these standards should be adopted in future economic analyses.
- Notably, the current evidence primarily originates from high-income countries, highlighting a gap in research within low-income settings
- Overall, this review highlights the reliance on varied methodological approaches and economic models, and suggests that future research could benefit from greater alignment with current clinical practices and broader geographic representation

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