Clinical Drug Investigation (2022) 42:643–656
https://doi.org/10.1007/s40261-022-01173-3

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Icosapent Ethyl, Evolocumab, Alirocumab, Ezetimibe, or Fenofibrate in Combination with Statins Compared to Statin Monotherapy

Daniel Tobias Michaeli[1,2,3] · **Julia Caroline Michaeli**[1,4] · **Tobias Boch**[2,3,5] · **Thomas Michaeli**[1,2,5]

Accepted: 16 June 2022 / Published online: 11 July 2022

Abstract

Background Despite treatment with statins, dyslipidaemia patients with elevated cholesterol- and triglyceride-levels remain at high residual risk for major adverse cardiovascular events (MACE). New lipid-lowering drugs must prevent the occurrence of MACE and exhibit cost-effectiveness for their successful adoption to clinical practice.

Objective To assess the cost effectiveness of icosapent ethyl, fenofibrate, ezetimibe, evolocumab, and alirocumab in combination with statins compared to statin monotherapy for cardiovascular prevention from the perspective of UK's National Health Service.

Methods A Markov model simulated the progression of cardiovascular disease and MACE, including myocardial infarction, stroke, angina pectoris, and coronary revascularisation, in dyslipidaemia patients. The model was populated with cardiovascular outcome trial data for each drug. Cost and utility data were extracted from peer-reviewed literature. The incremental cost-effectiveness ratio (ICER) is reported per quality-adjusted life years (QALY) gained in 2021 Great Britain Pounds (£).

Results For primary cardiovascular prevention, icosapent ethyl increased QALYs by 0.79 and costs by £15,421 compared to statin monotherapy (ICER = £19,485/QALY). Fenofibrate yielded 0.62 additional QALYs at cost-savings of − £6127 (ICER = − £9932/QALY). For secondary prevention, the omega-3 fatty acid icosapent ethyl extended QALYs by 0.98 at costs of £12,981 compared to statin monotherapy (ICER = £13,285/QALY). Fenofibrate added 0.85 QALYs whilst saving − £637 (ICER = − £7472/QALY). Ezetimibe increased QALYs by 0.60 at cost reductions of − £2529 (ICER = − £4231/QALY). PCSK9 inhibitors provided QALYs of 0.53 and 0.86 at costs of £45,279 and £46,375 for evolocumab (ICER = £85,193/QALY) and alirocumab (ICER = £54,211/QALY), respectively. At a willingness-to-pay threshold of £25,000/QALY, there is a probability of 100% for icosapent ethyl (98% in primary prevention) and 0% for PCSK9 inhibitors to be cost effective in secondary prevention.

Conclusions Icosapent ethyl is cost effective for primary and secondary cardiovascular prevention at an annual price of £2064 in the UK. For PCSK9 inhibitors, price discounts or prescription restrictions are necessary to achieve cost effectiveness.

✉ Daniel Tobias Michaeli
danielmichaeli@yahoo.com

1 Fifth Department of Medicine, University Hospital Mannheim, Heidelberg University, Mannheim, Germany

2 Department of Personalized Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany

3 Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany

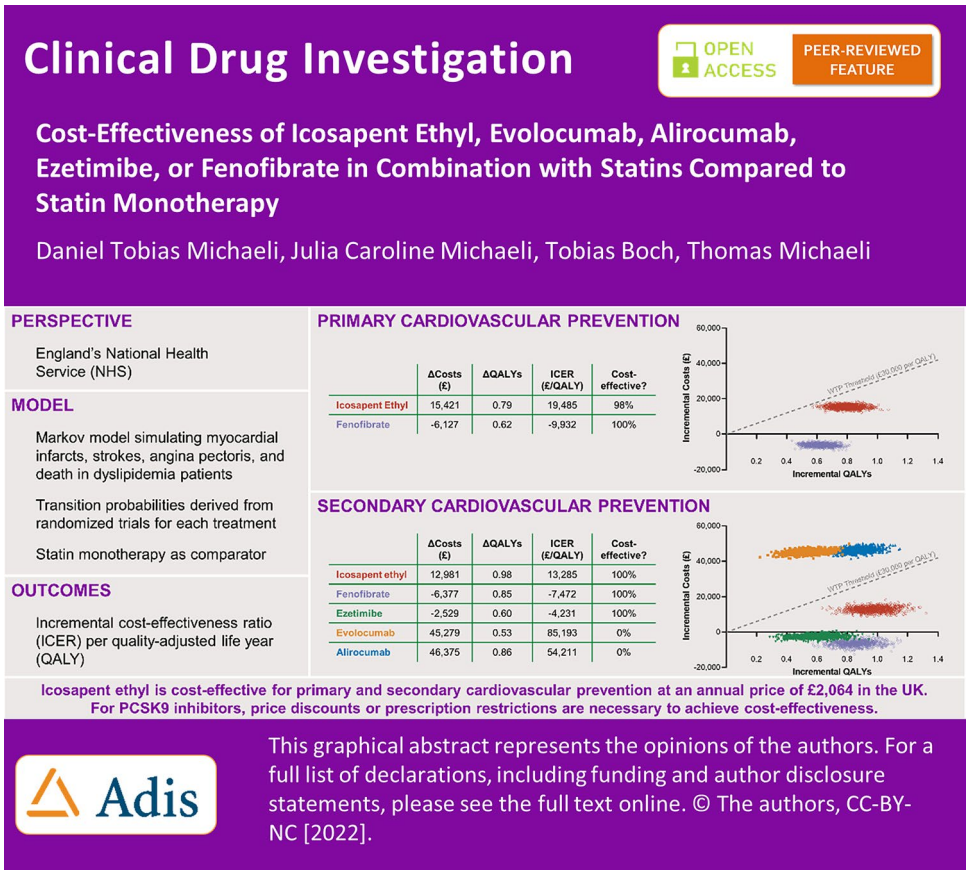
4 Department of Obstetrics and Gynecology, Asklepios-Clinic Hamburg Altona, Asklepios Hospital Group, Hamburg, Germany

5 Division of Personalized Medical Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

1 Introduction

Every third death is caused by atherosclerosis and resulting cardiovascular diseases (CVD) in the UK (2018) [1]. Consequently, there remains a pertinent need to prevent the incidence of CVD and its fatal events such as myocardial infarction (MI) and stroke. The European Society of Cardiology (ESC) recommends lifestyle modification and subsequently pharmacological therapy to reduce cardiovascular risk factors among high-risk patients, including arterial hypertension, diabetes mellitus, and dyslipidaemia [2]. Dyslipidaemia patients are commonly treated with statins. Despite treatment with high-intensity statins, patients continue to be exposed to significant residual risk for cardiovascular events

Graphical abstract



Key Points

Recently, the triglyceride-lowering omega-3 fatty acid icosapent ethyl and the low-density-lipoprotein-cholesterol-lowering (LDL-C) PCSK9 inhibitors evolocumab and alirocumab emerged as add-on statin treatments to reduce the risk of acute cardiovascular events in dyslipidaemia patients.

The developed Markov model reveals that icosapent ethyl is cost effective for primary and secondary cardiovascular prevention, whilst PCSK9 inhibitors are not.

Subgroup analyses demonstrate especially favourable clinical economics in high-risk populations, e.g., patients with elevated LDL-C levels (≥ 100 mg/dL or 2.6 mmol/L) for PCSK9 inhibitors or patients with elevated triglycerides (≥ 200 mg/dL or 2.3 mmol/L) and low high-density-lipoprotein-cholesterol (HDL-C) levels (≤ 35 mg/dL or 0.9 mmol/L) for icosapent ethyl.

in addition to safety concerns surrounding high statin doses [3, 4]. As a result, additive lipid-lowering therapies have been developed to further reduce the risk of major adverse cardiovascular events (MACE) [5–10].

The ESC categorises additive lipid-modifying drugs according to their primary effect on low-density lipoprotein cholesterol (LDL-C) and triglycerides [11]. Both indicators function as independent markers to detect at-risk patients [12, 13]. Whilst ezetimibe, evolocumab, and alirocumab predominantly impact LDL-C levels (cholesterol-lowering strategy), icosapent ethyl and fenofibrate mainly lower triglycerides (triglyceride-lowering strategy) [5–8, 10, 11]. Nonetheless, statins and icosapent ethyl exert beneficial pleiotropic effects on molecular pathways beyond lipid modification to achieve the MACE risk reduction observed in clinical trials [8, 14].

Novel pharmacological treatments must demonstrate not only efficacy, but also economic value to patients and insurers for successful adoption to clinical practice [2]. Public Health England estimates that 6% (£7.4 billion) of

the National Health Service's (NHS) annual healthcare budget is spent on CVD [15], which further increases pressure to introduce cost-effective prevention strategies. Previous cost-effectiveness analyses ordinarily evaluated single lipid-lowering drugs for secondary prevention in countries around the world [16–22]. The present study assesses the cost effectiveness of icosapent ethyl, fenofibrate, ezetimibe, evolocumab, and alirocumab in combination with moderate-/high-intensity statins compared to moderate-/high-intensity statin monotherapy for primary and secondary cardiovascular prevention from the perspective of the NHS. To the best of our knowledge, this is the first study evaluating the cost effectiveness of icosapent ethyl in the UK.

2 Data and Methods

2.1 Model Structure

A Markov model simulating the progression of CVD in dyslipidaemia patients was adapted from existing cost-effectiveness studies (Fig. 1) [23]. Patients transitioned between three distinct health states: "Alive without CVD", "Alive with CVD", and "Dead". The occurence of non-fatal MI and non-fatal strokes transitioned patients without prior CVD history to the "Alive with CVD" state. Within each health state, patients were at risk of acute events, including coronary revascularisation and hospitalisation for unstable angina pectoris. Patients without CVD entered the model in the "Alive without CVD" state (primary prevention cohort), whereas patients with documented CVD commenced in the "Alive with CVD" state (secondary prevention cohort). Patients were channelled to the "Dead" state by dying from CVD or non-CVD causes. The model was constructed from the perspective of the UK's NHS, entailing a 20-year time horizon (lifetime) and a 3.5% (± 1.5%) discount rate [24].

2.2 Evaluated Treatment Options

For the purpose of our analyses, we considered all lipid-lowering therapies that were approved by the European Medicines Agency (EMA) for primary or secondary cardiovascular prevention after the introduction of statins. Nicotinic acid in combination with laropiprant was excluded based on a negative EMA recommendation after the results of the HPS2-THRIVE study in 2013 [9]. For each drug, we selected the largest cardiovascular outcomes trial (CVOT) in dyslipidaemia patients (Supplementary Table e1). We therefore considered five drugs (ezetimibe, icosapent ethyl, evolocumab, alirocumab, fenofibrate) in our analyses. Only icosapent ethyl and fenofibrate were analysed for primary cardiovascular prevention as ezetimibe, evolocumab, and alirocumab were not yet evaluated in patients without established CVD. Until this point there were no completed CVOT for bile acid sequestrants, inclisiran, bempedoic acid, and other investigational new drugs.

2.3 Comparator

The European Society of Cardiology guidelines recommend to escalate lipid-lowering treatments from moderate-/high-intensity statins to moderate-/high-intensity statins in combination with an adjunct therapeutic for patients with refractory elevated blood lipids [11]. Therefore, moderate-/high-intensity statin monotherapy, e.g., simvastatin (20–40 mg), atorvastatin (40–80 mg), rosuvastatin (20–40 mg), was set as the comparator. This also reflects the average baseline patient population in each drug's underlying CVOT (Supplementary Table e1).

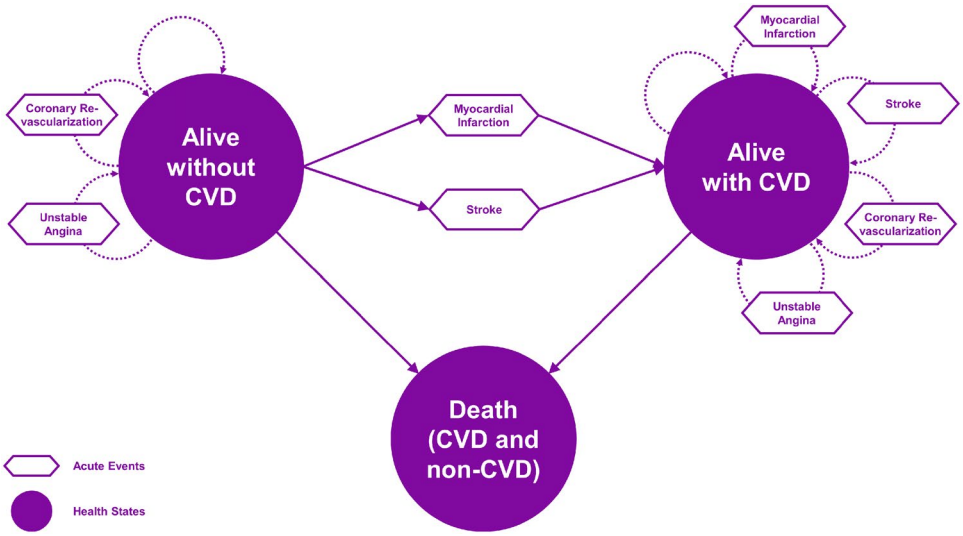


Fig. 1 Markov model structure of cardiovascular diseases progression and acute events. Patients commence the model in the "Alive without CVD" (primary prevention) or "Alive with CVD" (secondary prevention) state. Every year patients were at risk of experiencing acute cardiovascular events (myocardial infarction, stroke, coronary revascularisation, unstable angina pectoris) and dying from CVD or non-CVD causes. Model structure adopted from Michaeli et al. [23]. *CVD* cardiovascular disease

2.4 Transition Probabilities

Transition probabilities were calculated based on the CVOT results for icosapent ethyl (REDUCE-IT), evolocumab (FOURIER), alirocumab (ODYSSEY), ezetimibe (IMPROVE-IT), and fenofibrate (ACCORD) [5–8, 10]. First, hazard ratios for each acute event, non-CVD death, and CVD death were extracted from the respective trials (Table 1). Second, endpoints were converted to annual transition probabilities using the median follow-up of each CVOT (Supplementary Table e2), coherent with previous cost-effectiveness studies [16, 25].

For icosapent ethyl and fenofibrate, CVOT reported distinct endpoints in patients with and without established CVD. Consequently, separate transition probabilities for primary and secondary cardiovascular prevention were estimated based on the underlying CVD prevalence, the overall MACE reduction, and the occurrence of acute events in patients with and without established CVD [16]. For ezetimibe, evolocumab, and alirocumab, CVOT only reported endpoints in patients with established CVD. Therefore, these therapies were only evaluated for secondary cardiovascular prevention setting. Similar to previous studies, baseline transition probabilities were multiplied by + 10% and + 14% annually to model the age-dependent increased risk of non-CVD and CVD events, respectively [23].

2.5 Model Population

Patients commenced the simulation at 63 years of age, which equals to the weighted-average age of the patient population studied in all considered CVOT.

2.6 Costs

The healthcare expenditure of cardiovascular events in patients with dyslipidaemia was obtained from peer-reviewed literature. Costs for the "Alive without CVD" state of £2497 per year were based on healthcare expenditure in dyslipidaemia patients without history of any cardiovascular event [26]. These costs are based on a retrospective cohort study of 24,093 patients over 6 years in the UK. Costs for acute events amounted to £7842 for non-fatal MI, £11,512 for non-fatal stroke, £3517 for unstable angina, and £7337 for coronary revascularisation [27, 28]. Spending for the "Alive with CVD" state of £3466 per year was based on the treatment cost of patients with established CVD, e.g., after MI, stroke, angina pectoris, and associated comorbidities, e.g., arterial hypertension, diabetes mellitus, and chronic kidney diseases [27, 28]. Costs for non-CVD deaths were estimated at £2734 based on the NHS expense during the last 90 days of life weighted by the location of death [29, 30]. The incremental cost of dying from CVD compared to non-CVD causes was estimated at £3558 [28]. All costs are presented in 2021 Great British Pounds (£).

List prices for all lipid-lowering drugs were obtained from the British National Formulary to calculate annual treatment costs [31], which amounted to £357 for statin (weighted-average cost of generic statins for high-intensity treatment), £346 for ezetimibe, £2064 for icosapent ethyl (manufacturer guidance), £4423 for evolocumab, £4412 for alirocumab, and £141 for fenofibrate.

2.7 Utilities

Health-related quality of life (HRQoL) values, measured by the EQ-5D-5L index, were assigned to each health state. Patients in the "Alive without CVD" state were assigned an average age-specific HRQoL value of the overall English population obtained from the longitudinal General Practice Patient Survey (GPPS) with 1,416,793 responses [32]. The HRQoL was reduced by − 0.08 in the "Alive with CVD" state [33]. A HRQoL of 0 was allocated to the "Dead" state. HRQoL values were further reduced contingent on the incidence of acute cardiovascular events: − 0.04 for non-fatal MI, − 0.12 for non-fatal stroke, − 0.09 for hospitalisation for angina, and − 0.01 for coronary revascularisation [16].

2.8 Outcomes

We calculated the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life years (QALY) and life years (LY) for each adjunct lipid-lowering drug compared to statin monotherapy. We also contrasted numbers needed to treat (NNT) for each cardiovascular event across treatment alternatives.

2.9 Sensitivity, Scenario, Willingness-to-Pay, and Pricing Analyses

Several sensitivity analyses were conducted to assess the robustness of calculated outcomes. First, a univariate (deterministic) sensitivity analysis evaluates the impact of variations in a distinct input parameter on ICERs. Variability in drug prices, discount rates, time horizon, and mortality trends were assessed in a scenario analysis. Drugs' differential efficacy in patient populations was explored in a subgroup analysis. A probabilistic sensitivity analysis (PSA) evaluates the impact of simultaneous variations in input parameters on results. Base case point estimates were therefore sampled 1000 times from their defined distribution (Table 1) to estimate 95% confidence intervals (CI) for ICERs. Based on the PSA, we estimated the probability that a treatment is cost effective at the UK's willingness-to-pay (WTP) threshold of £20,000 to £30,000 per QALY. Finally,

Table 1 Input parameters and distribution for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate: hazard ratios, costs, utilities, and others

	Cholesterol-lowering strategy			Triglyceride-lowering strategy		Distribution	References
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fenofibrate		
Hazard ratios							
Alive without CVD (primary prevention)							
Non-fatal MI	NA[a]	NA[a]	NA[a]	0.78 (0.67–0.90)	0.98 (0.84–1.13)	Normal	[5–8, 10]
CVD death	NA[a]	NA[a]	NA[a]	0.90 (0.77–1.04)	0.92 (0.78–1.06)	Normal	[5–8, 10]
Non-CVD death	NA[a]	NA[a]	NA[a]	1.14 (0.97–1.31)	1.03 (0.87–1.18)	Normal	[5–8, 10]
Non-fatal stroke	NA[a]	NA[a]	NA[a]	0.81 (0.69–0.93)	1.13 (0.96–1.29)	Normal	[5–8, 10]
Hospitalisation for unstable angina	NA[a]	NA[a]	NA[a]	0.76 (0.64–0.87)	1.05 (0.89–1.21)	Normal	[5–8, 10]
Coronary revascularisation	NA[a]	NA[a]	NA[a]	0.76 (0.64–0.87)	1.06 (0.90–1.21)	Normal	[5–8, 10]
Alive with CVD (secondary prevention)							
Non-fatal MI	0.87 (0.80–0.95)	0.72 (0.64–0.81)	0.86 (0.77–0.96)	0.68 (0.58–0.79)	0.88 (0.75–1.01)	Normal	[5–8, 10]
CVD death	1.00 (0.89–1.13)	1.05 (0.88–1.25)	0.88 (0.74–1.05)	0.79 (0.67–0.91)	0.82 (0.70–0.95)	Normal	[5–8, 10]
Non-CVD death	0.98 (0.90–1.06)	1.04 (0.91–1.19)	0.78 (0.66–0.94)	1.01 (0.85–1.16)	0.92 (0.79–1.06)	Normal	[5–8, 10]
Non-fatal stroke	0.86 (0.73–1.00)	0.91 (0.78–1.07)	0.73 (0.57–0.93)	0.71 (0.60–0.82)	1.01 (0.86–1.17)	Normal	[5–8, 10]
Hospitalisation for unstable angina	1.06 (0.85–1.33)	0.99 (0.82–1.18)	0.61 (0.41–0.92)	0.67 (0.57–0.77)	0.94 (0.80–1.08)	Normal	[5–8, 10]
Coronary revascularisation	0.96 (0.90–1.02)	0.78 (0.71–0.86)	0.88 (0.79–0.97)	0.66 (0.56–0.75)	0.94 (0.80–1.08)	Normal	[5–8, 10]
Costs							
Annual treatment cost	346	4467	4.412	2064	141	Fixed	[31]
Annual statin cost	357					Fixed	[31]
Alive without CVD	2497 (± 25%)					Gamma	[26]
Alive with CVD	3466 (± 25%)					Gamma	[5–8, 10, 26]
Non-fatal MI	7842 (± 25%)					Gamma	[27, 28]
Non-fatal stroke	11,512 (± 25%)					Gamma	[27, 28]
Hospitalisation for unstable angina	3517 (± 25%)					Gamma	[26]
Coronary revascularisation	7337 (± 25%)					Gamma	[26]
Non-CVD death	2734 (± 25%)					Gamma	[29, 30]
CVD death	6291 (± 25%)					Gamma	[27–30]
Utilities							
Alive without CVD							
65–70 years	0.7395 (0.7385–0.7415)					Beta	[32]
70+ years	0.6745 (0.6725–0.6770)					Beta	[32]
Alive with CVD							
65–70 years	0.6595 (0.6585–0.6615)					Beta	[32, 33]
70+ years	0.5945 (0.5925–0.5970)					Beta	[32, 33]
Decrements							
Non-fatal MI	0.04 (0.02–0.05)					Gamma	[49]
Non-fatal stroke	0.12 (0.09–0.16)					Gamma	[49]
Hospitalisation for unstable angina	0.09 (0.06–0.13)					Gamma	[49]
Coronary revascularisation	0.01 (0.01–0.03)					Gamma	[49]
Others							
Discount rate	3.5% (2–5)					Fixed	[24]

Table 1 (continued)

	Cholesterol-lowering strategy			Triglyceride-lowering strategy		Distribution	References
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fenofibrate		
Annual CVD risk increase	14% (12–14)					Fixed	[23]
Annual non-CVD risk increase	10% (8–12)					Fixed	[23]
Cohort	1000 patients					Fixed	Assumption
Starting age	63 years					Fixed	[5–8, 10]
Time horizon	Lifetime: 20 years					Fixed	[24]

The Table presents base case input parameters regarding hazard ratios, costs, utilities, and others for evaluated lipid-lowering therapies. Deterministic and probabilistic sensitivity analyses were conducted based on variations displayed in brackets and their defined distribution. Transition probabilities were derived from displayed hazard ratios combined with each trial's follow-up period as illustrated in Supplementary Table e2. Lipid-lowering drugs are presented as cholesterol-and triglyceride-lowering according to guideline recommendations [11]. Costs in 2021 Great Britain Pounds (£)

CVD cardiovascular disease, *MI* myocardial infarction

[a]No clinical trials reporting major cardiovascular adverse events for patients without established CVD were available for ezetimibe, evolocumab, and alirocumab

the impact of drug prices on the calculated ICERs was investigated in a pricing analysis.

3 Results

Base case results are presented and thereafter scrutinised in a variety of sensitivity, scenario, and subgroup analyses.

3.1 Base Case Analysis

3.1.1 Cholesterol-Lowering Strategy

Figure 2 visualises the results of base case ICERs per QALY gained on a cost-effectiveness plane. Ezetimibe increased QALYs gained by 0.60 at cost reductions of − £2529 compared to statin monotherapy for secondary cardiovascular prevention (ICER = − £4231 per QALY). Protein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors provided incremental QALYs of 0.53 and 0.86 at costs of £45,279 and £46,375 for evolocumab (ICER = £85,193 per QALY) and alirocumab (ICER = £54,211 per QALY), respectively. Incremental LYs gained were 0.80 for ezetimibe, 0.60 for evolocumab, and 1.14 for alirocumab. Number needed to treat was lower for PCSK9 inhibitors compared to ezetimibe across all cardiovascular endpoints.

3.1.2 Triglyceride-Lowering Strategy

Regarding primary prevention, icosapent ethyl increased QALYs by 0.79 and costs by £15,421 compared to statin monotherapy (ICER = £19,485 per QALY). Fenofibrate yielded 0.62 additional QALYs at incremental cost-savings of − £61,267 (ICER = − £9932 per QALY). Supplementary Figure e1 demonstrates that icosapent ethyl provided greater LYs gained than fenofibrate (0.90 vs 0.84). Number needed to treat was lower for icosapent ethyl in MI, stroke, and CVD death prevention, yet not unstable angina, coronary revascularisation, and non-CVD death prevention relative to fibrate.

In secondary prevention, icosapent ethyl extended QALYs by 0.98 for patients at costs of £12,981 compared to statin monotherapy (ICER = £13,285 per QALY). Fenofibrate added 0.85 QALYs whilst saving − £6377 (ICER = − £7472 per QALY). Life-years gained were similar for icosapent ethyl and fenofibrate (1.25 vs 1.28). Fewer patients were needed to treat with icosapent ethyl relative to fenofibrate to prevent all MACE (Table 2).

3.2 Sensitivity Analyses

Univariate, scenario, probabilistic, WTP, and pricing analyses were conducted to evaluate the robustness of base case results under varying input values and different settings.

3.2.1 Univariate Sensitivity and Scenario Analyses

Univariate sensitivity analysis demonstrates that ICERs are mainly influenced by the transition probability from the "Alive with CVD" to "Death" state and attributed costs as well as the incidence of acute cardiovascular events (Tornado plots in Supplementary Figure e2 and e3). Scenario analysis shows that a ± 1.5% variation in the discount rate causes an average fluctuation of ± 7% in ICERs (Supplementary Table e3). A ± 2% uncertainty surrounding the

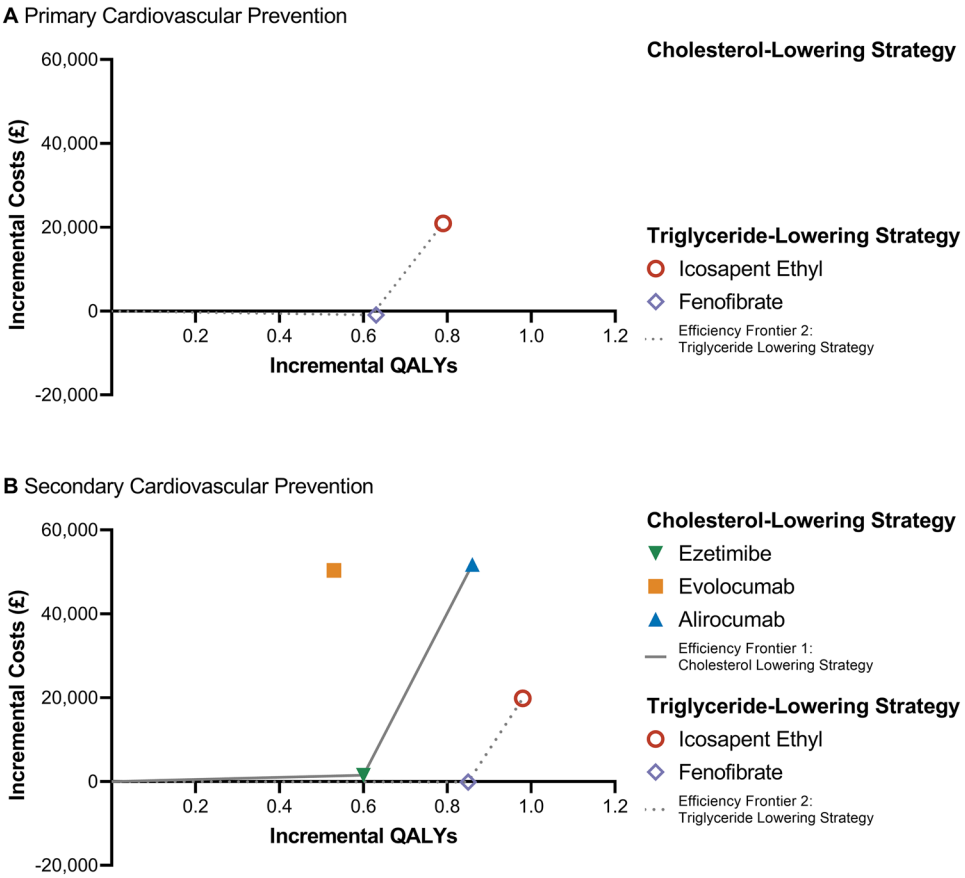


Fig. 2 Cost-effectiveness plane for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (**A**) and secondary (**B**) cardiovascular prevention. QALYs and costs presented for the average person simulated in the model. Lipid-lowering drugs are presented as cholesterol-and triglyceride-lowering according to guideline recommendations [11]. Costs in 2021 Great Britain Pounds (£). *QALY* quality-adjusted life year

annual CVD risk increase, caused an average ± 6% variation in ICERs.

3.2.2 Subgroup Analyses

All drugs displayed differential efficacy outcomes in their clinical trials. Consequently, ICERs were assessed for a variety of patient populations (Table 3). Compared to the overall population, icosapent ethyl was especially cost effective among patients aged < 65 years for both primary (ICER = £14,368 per QALY) and secondary (ICER = £8809 per QALY) cardiovascular prevention. Patient age did not significantly impact ICERs for PCSK9 inhibitors. The ICER of icosapent ethyl was lower among patients with baseline triglycerides of ≥ 200 mg/dL (≥ 2.3 mmol/L) and HDL-C levels of ≤ 35 mg/dL (≤ 0.9 mmol/L) for primary (ICER = £12,166 per QALY) and secondary (ICER = £7131 per QALY) cardiovascular prevention. Accordingly, the targeted treatment of patients with baseline LDL-C of ≥ 100 mg/dL (≥ 2.6 mmol/L) reduced the ICERs of evolocumab (ICER = £63,600 per QALY) and alirocumab (ICER = £44,851 per QALY). ICERs were lower for icosapent ethyl and PCSK9 inhibitors in patients with a baseline high-sensitivity CRP lower than ≤ 2 mg/L.

3.2.3 Probabilistic Sensitivity Analyses

Input parameters were drawn from their defined distribution across CIs displayed in Table 1 for 1000 iterations. Incremental QALYs and costs of these 1000 resamples are visualised on a cost-effectiveness plane in Fig. 3.

For the cholesterol-lowering strategy, QALYs gained were significantly higher for alirocumab (0.86, 95% CI 0.72–1.00) than for evolocumab (0.53, 95% CI 0.40–0.67, $p < 0.001$) and ezetimibe (0.60, 95% CI 0.43–0.77, $p < 0.001$) in secondary prevention. The ICER of alirocumab and evolocumab remained robust at £54,703 (95% CI 46,737–63,565) and £87,062 per QALY (95% CI 67,690–111,250), respectively.

For the triglyceride-lowering strategy, QALY gains were consistently higher for icosapent ethyl (0.80, 95% CI 0.68–0.92) than fenofibrate (0.62, 95% CI 0.51–0.73, $p < 0.001$) in patients without established CVD. For secondary prevention, icosapent ethyl offered QALY gains of 0.97 (95% CI 0.82–1.14) compared to 0.86 (95% CI 0.70–1.03, $p < 0.001$) for fenofibrate. The ICER of icosapent ethyl remained robust at £19,544 per QALY (95% CI 15,843–23,586) for primary prevention and at £13,402 per QALY (95% CI 10,379–16,469) for secondary prevention.

Table 2 Base case LYs, QALYs, ICERs, and NNT for primary and secondary cardiovascular prevention

	Cholesterol-lowering strategy			Triglyceride-lowering strategy	
	Ezetimibe	Evolocumab	Alirocumab	Icosapent ethyl	Fenofibrate
Primary prevention					
Incremental LYs	[a]	[a]	[a]	0.90	0.84
Incremental QALYs	[a]	[a]	[a]	0.79	0.62
Incremental costs (£)	[a]	[a]	[a]	15,421	− 6167
ICER (£ per LY)	[a]	[a]	[a]	17,121	− 7356
ICER (£ per QALY)	[a]	[a]	[a]	19,485	− 9932
Number needed to treat (NNT)					
Non-fatal MI	[a]	[a]	[a]	1.6	3.3
Non-fatal stroke	[a]	[a]	[a]	5.6	16.3
Hospitalisation for unstable angina	[a]	[a]	[a]	4.6	4.4
Coronary revascularisation	[a]	[a]	[a]	1.3	1.2
CVD death	[a]	[a]	[a]	3.9	5.0
Non-CVD death	[a]	[a]	[a]	41.7	17.5
Secondary prevention					
Incremental LYs	0.80	0.60	1.14	1.25	1.28
Incremental QALYs	0.60	0.53	0.86	0.98	0.85
Incremental costs (£)	− 2529	45,279	46,375	12,981	− 6377
ICER (£ per LY)	− 3157	75,283	40,708	10,409	− 4998
ICER (£ per QALY)	− 4231	85,193	54,211	13,285	− 7472
Number needed to treat (NNT)					
Non-fatal MI	2.7	1.6	1.6	1.5	3.5
Non-fatal stroke	8.8	6.4	6.4	5.3	21.5
Hospitalisation for unstable angina	31.3	5.8	14.1	4.3	5.2
Coronary revascularisation	1.7	1.1	1.4	1.1	1.3
CVD death	7.3	6.4	4.5	3.8	5.2
Non-CVD death	15.8	24.3	17.9	48.8	23.1

The Table presents base case LYs, QALYs, ICERs, and NNT for a patient commencing respective lipid-lowering therapy at the age of 63 years until end-of-life. Lipid-lowering drugs are presented as cholesterol- and triglyceride-lowering according to guideline recommendations [11]. Costs in 2021 Great Britain Pounds (£)

CVD cardiovascular disease, *ICER* incremental cost-effectiveness ratio, *LY* life year, *MI* myocardial infarction, *NA* not applicable, *NNT* number needed to treat, *QALY* quality-adjusted life year

[a]No clinical trials reporting major cardiovascular adverse events for patients without established CVD were available for ezetimibe, evolocumab, and alirocumab

3.2.4 Willingness-to-Pay and Pricing Analyses

In primary prevention, fenofibrate was cost effective across all WTP thresholds (Fig. 4). Icosapent ethyl surpassed a 95% probability of cost effectiveness at a WTP of £24,000 per QALY. Assuming a WTP of the National Institute for Health and Care Excellence of £25,000 per QALY, icosapent ethyl was cost effective 98% of times—at a WTP of £30,000 per QALY, icosapent ethyl was cost effective across all simulations for secondary prevention. We estimated a maximum list price of £2704 for icosapent ethyl to maintain cost-effectiveness, representing a +31% premium to the list price of £2064 proposed by the manufacturer (Supplementary Fig. e4).

In secondary prevention, the generic drugs ezetimibe and fenofibrate were cost effective compared to statin monotherapy across all WTP thresholds. Icosapent ethyl surpassed a 95% probability of cost effectiveness at a WTP threshold of £17,000 per QALY, alirocumab at a threshold of £64,000 per QALY, and evolocumab at a threshold of £112,000 per QALY. Consequently, icosapent ethyl was cost effective across 100% of simulations, whilst PCSK9 inhibitors were not cost-effective across any simulation at the UK's WTP of £30,000 per QALY. We therefore estimated a maximum list price of £3402 for icosapent ethyl, which represents a + 65% increase compared to manufacturer guidance. In contrast, discounts of − 37 to − 53% are necessary to achieve cost

Table 3 Subgroup analysis

Subgroup	Primary prevention	Secondary prevention		
	Icosapent ethyl	Icosapent ethyl	Evolocumab	Alirocumab
Base case	19,485	13,285	85,193	54,211
Age				
< 65 years	14,368	8809	88,474	59,567
≥ 65 years	36,383	37,071	85,193	47,632
Baseline triglyceride ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL[a]				
No	23,288	17,226	NR	NR
Yes	12,166	7131	NR	NR
Baseline LDL-C ≥ 100 mg/dL[b]				
No	NR	NR	107,362	62,001
Yes	NR	NR	63,600	44,851
Baseline high-sensitivity CRP				
≤ 2 mg/L	14,882	9221	74,106	49,660
> 2 mg/LL	25,694	20,048	99,947	59,567

ICER (£ per QALY) are presented for different patient populations. Costs in 2021 Great Britain Pounds (£)

CRP c-reactive protein, *CVD* cardiovascular disease, *HDL-C* high-density-lipoprotein-cholesterol, *ICER* incremental cost-effectiveness ratio, *LDL-C* low-density-lipoprotein-cholesterol, *NR* not reported, *QALY* quality-adjusted life year

[a]A triglyceride level of 200 mg/dL is equivalent to 2.3 mmol/L. A HDL-C level of 35 mg/dL is equivalent to 0.9 mmol/LL

[b]A LDL-C level of 100 mg/dL is equivalent to 2.6 mmol/LL

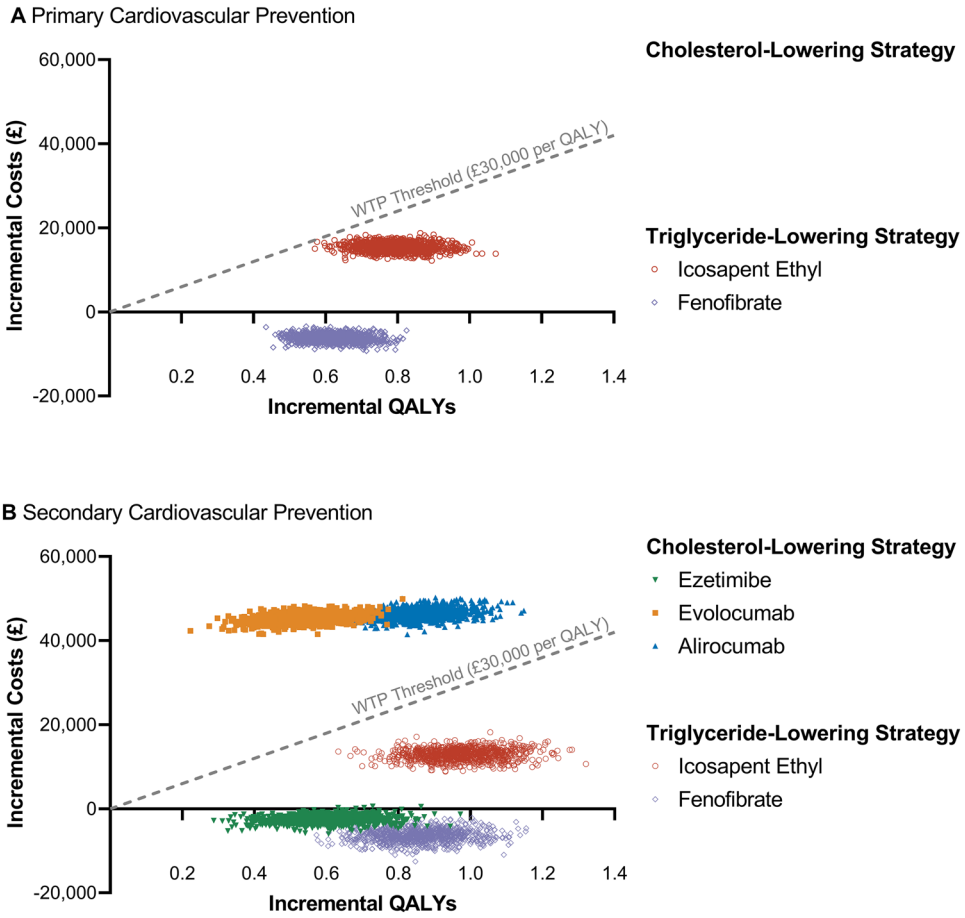


Fig. 3 Probabilistic sensitivity analysis for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (**A**) and secondary (**B**) cardiovascular prevention. Input parameters displayed in Table 1 were varied by their confidence intervals and distribution; 1000 simulations of this probabilistic sensitivity analysis are visualised in this Figure. The grey line illustrates the English NHS' upper willingness-to-pay threshold of £30,000 per QALY. Lipid-lowering drugs are presented as cholesterol- and triglyceride-lowering according to guideline recommendations [11]. QALYs and costs presented for the average person simulated in the model. Costs in 2021 Great Britain Pounds (£). *ICER* incremental cost-effectiveness ratio, *NHS* National Health Service, *QALY* quality-adjusted life year

effectiveness for alirocumab and evolocumab respectively, in the UK.

4 Discussion

Our study assesses the cost effectiveness of lipid-lowering therapies for primary and secondary cardiovascular prevention in the UK. Among cholesterol-lowering drugs, ezetimibe is cost effective for secondary prevention, whilst the PCSK9 inhibitors evolocumab and alirocumab are not. Price discounts beyond − 37% or the targeted treatment of patients with LDL-C levels beyond 100 mg/dL (2.6 mmol/L) are required for PCSK9 inhibitors to reach cost effectiveness. In contrast, both triglyceride-lowering drugs, icosapent ethyl and fenofibrate, are cost effective for patients with and without established CVD at the UK's WTP of £25,000 per QALY.

4.1 Cholesterol-Lowering Strategy: Ezetimibe, Evolocumab, and Alirocumab

Protein convertase subtilisin/kexin type 9 serine protease inhibitors reduce the risk of MACE by 15%, in contrast to an observed risk reduction of 6% provided by ezetimibe [5–7]. However, PCSK9 inhibitors are costly with list prices around £4400 per year in the UK, causing ICERs to exceed the NHS' established cost-effectiveness threshold of £20,000 to £30,000 per QALY. Consequently, PCSK9 inhibitors are a "double edged sword" in the treatment of dyslipidaemia patients. Whilst increasing available therapeutic options to patients, pharmaceutical companies demand steep prices for the limited observed efficacy [6].

Consistent with our results, the NHS concluded that both PCSK9 inhibitors are not cost effective at annual treatment costs around £4400 [34, 35]. The committee demanded discounts in undisclosed magnitude alongside prescribing restrictions. Our analyses suggest that discounts beyond − 37% are necessary for PCSK9 inhibitors

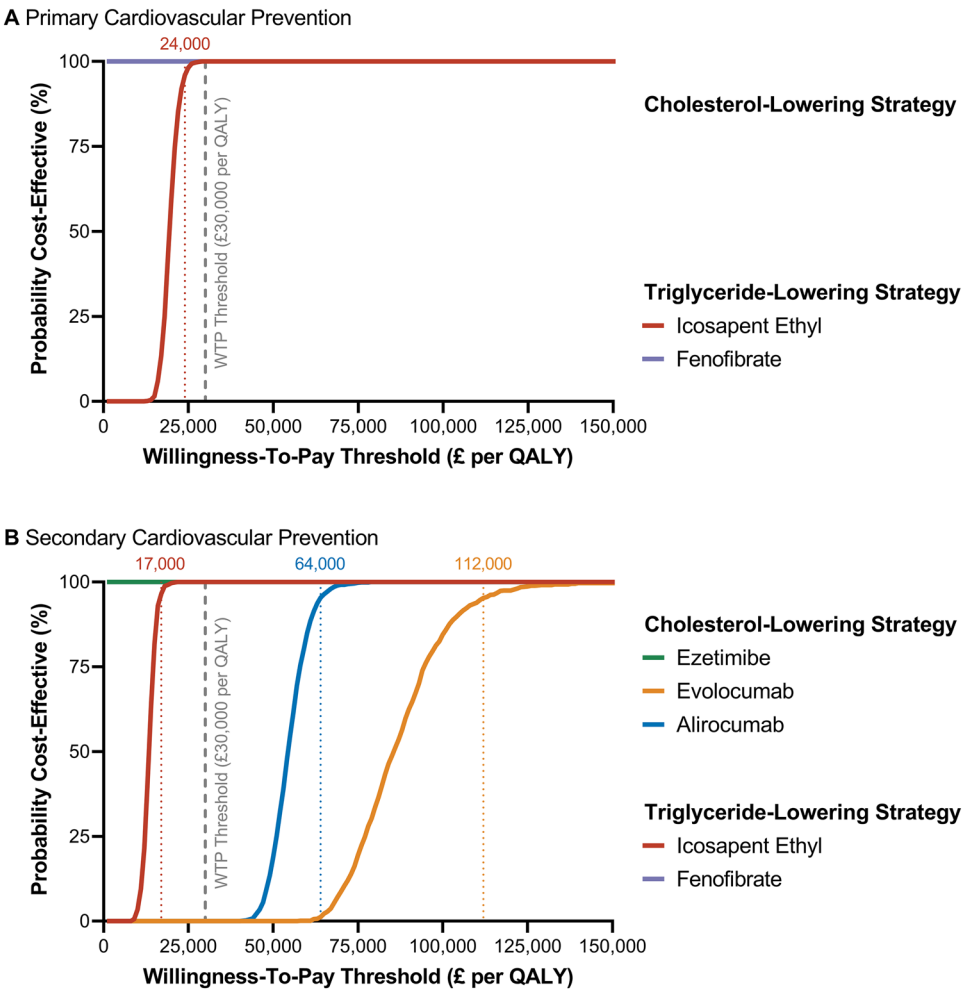


Fig. 4 Probability of cost effectiveness at different willingness-to-pay thresholds for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (**A**) and secondary (**B**) cardiovascular prevention. The grey line illustrates the English NHS' upper willingness-to-pay threshold of £30,000 per QALY. Dotted lines show the willingness-to-pay thresholds at which the probability of cost-effectiveness surpasses 95%. Lipid-lowering drugs are presented as cholesterol-and triglyceride-lowering according to guideline recommendations [11]. QALYs and costs presented for the average person simulated in the model. Costs in 2021 Great Britain Pounds (£) and willingness-to-pay thresholds in £/QALY. *NHS* National Health Service, *QALY* quality-adjusted life year

to be cost effective. Prescription is restricted to patients with established CVD, a high risk of acute cardiovascular events, and LDL-C levels above 135 mg/dL (3.5 mmol/L). Incremental cost-effectiveness ratios can be substantially lowered by reducing prices and restricting prescription to at-risk patients as analyses in the USA demonstrate [22, 36]. Similarly, our subgroup analysis demonstrates lower ICERs among patients with baseline LDL-C levels of ≥ 100 mg/dL for evolocumab (ICER = £63,600 per QALY) and alirocumab (ICER = £44,851 per QALY).

In line with our results, meta-analyses reviewing the cost effectiveness of lipid-lowering therapeutics across the globe concluded that ezetimibe is cost effective, in contrast to PCSK9 inhibitors, which are not cost-effective [25, 37–39]. Only one of ten studies (10%) evaluated PCSK9 inhibitors as cost effective, compared to five out of eight (63%) for ezetimibe [25]. Previous studies required discounts of − 20% to − 88% on PCSK9 inhibitors' list prices to achieve cost effectiveness [39]. Although the clinical economics of PCSK9 inhibitors are well established in developed nations, evidence from low-income countries is scarce [37].

4.2 Triglyceride-Lowering Strategy: Icosapent Ethyl and Fenofibrate

The REDUCE-IT and JELIS trials alongside recent meta-analyses demonstrate that icosapent ethyl reduces the risk of MACE by up to 25% in patients with elevated triglyceride levels despite statin therapy in a dose-dependent manner [8, 40, 41]. Informed by these CVOT, studies evaluated the cost-effectiveness of icosapent ethyl in Germany, the USA, Australia, Canada, and Japan [16–21, 23].

In Germany, Michaeli et al assessed icosapent ethyl as a cost-effective use of resources compared to statin monotherapy based on ICERs of €18,133 per QALY for primary and €14,485 per QALY for secondary cardiovascular prevention [23]. The US Institute for Clinical and Economic Review and Weintraub et al concluded icosapent ethyl is cost effective at the US WTP threshold of USD50,000 per QALY with ICERs ranging from USD18,000 to 36,118 per QALY [17, 19]. Ademi et al considered icosapent ethyl cost effective at the Australian WTP threshold of AUD50,000 per QALY, especially for secondary prevention [16]. They calculated an ICER of AUD45,036 per QALY using a Markov model simulation based on annual treatment costs of AUD1637. In contrast, Gao et al calculated an ICER of AUD59,036 per QALY based on annual treatment costs of AUD3768 [18].

Similar to Australia, icosapent ethyl's clinical economics remain disputed in Canada. Lachaine et al calculated an ICER of CAD42,797 per QALY, whilst the Canadian Agency for Drugs and Technologies in Health (CADTH) calculated an ICER of CAD105,053 per QALY and therefore demanded a price discount of − 43% to reach the Canadian WTP threshold of CAD50,000 per QALY [20, 21]. Kodera et al assessed icosapent ethyl as cost effective for primary, yet not secondary prevention in Japan [42]. However, they derive transition probabilities based on a MACE reduction of 19% observed in the Japanese JELIS trial, which treated patients with 1.8 g eicosapentaenoic acid (EPA) per day [40, 42]. Consequently, icosapent ethyl's ICER is likely lower at treatment doses of 4 g per day in Japan considering the observed dose-dependent MACE reduction [41].

Cost-effectiveness studies conducted in Germany, the USA, Australia, Canada, and Japan are coherent with our results in the UK. Icosapent ethyl is cost effective for cardiovascular prevention at the UK's WTP of £25,000 per QALY. The clinical and economic value is especially favourable in secondary prevention (ICER = £13,285 per QALY). Furthermore, the conducted subgroup analysis demonstrates that an early therapeutic intervention in patients younger than 65 years substantially lowers ICERs. Additionally, targeting at-risk patients with elevated triglycerides (≥ 200 mg/dL) at low HDL-C levels (≤ 35 mg/dL) reduces icosapent ethyl's ICERs.

Fenofibrate is an off-patent drug that is available for £141 per year, yet yields additional QALY and LY gains for patients. Consequently, their observed negative ICERs were expected. Clinicians must consider the economic savings that generic drugs offer to the healthcare system in their prescription behaviour.

4.3 Limitations

First, long-term efficacy data are not available for all considered lipid-lowering drugs. We therefore derived annual transition probabilities from aforementioned CVOT with follow-up periods between 2.2 and 6.0 years (Supplementary Table 1), subsequently applied them to a 20-year time horizon, and considered age-specific trends by employing annually increasing CVD risks. Whilst this methodology is widely used in cost-effectiveness studies [16, 25], CVOT with longer follow-up periods are necessary to determine the efficacy and cost of lipid-lowering drugs in clinical practice.

The REDUCE-IT trial compared icosapent ethyl versus mineral oil, raising scientific debate about the potentially overestimated MACE reduction of 25%, which may overvalue its calculated ICER [8, 43]. Nonetheless, icosapent ethyl's efficacy is underlined by the US Food and Drug Administration (FDA) and EMA regulatory approval.

Our analyses were conducted from the perspective of the UK NHS. Utilities, costs, and WTP thresholds in other countries may vary as previously discussed.

Previous studies evaluated the cost effectiveness of cholesterol-lowering drugs by estimating transition probabilities from national CV observation studies to then simulate each drug's risk reduction in MACE based on its effect on the

surrogate parameter LDL-C. In contrast, we derived transition probabilities and MACE risk reductions from CVOT to adequately capture each drug's pleiotropic metabolic effects beyond lowering blood lipids, which are particularly important for triglyceride-lowering drugs [8, 10].

Our Markov model assumes immediate treatment intensification. In clinical practice, there remains a significant delay in the intensification and initiation of lipid-lowering treatments, resulting in worse CV outcomes and higher ICER estimates [44].

Finally, adverse events were not considered in our model. Future analyses should evaluate the clinical economics of triple and quadruple lipid-modifying agents. Moreover, the efficacy and costs of therapy sequence require further investigation, given their importance for physicians in clinical practice.

4.4 Future Research

Coherent with previous meta-analyses [45, 46], this study highlights the lack of CVOT data for the use of ezetimibe and PCSK9 inhibitors in primary cardiovascular prevention. Recent market access strategies reveal that pharmaceutical companies first develop new lipid-modifying agents for rare high-risk patient populations, e.g., familial hypercholesterolaemia. This strategy permits companies to finance costly CVOT, which require the enrolment of several thousand patients, for the secondary CV prevention indication. However, companies may be reluctant to fund further CVOT for primary CV prevention, as the lower efficacy in this indication could lead to insurers demanding rebates on a drug's overall price. Ultimately, this results in unmet needs of robust trials evaluating the efficacy of lipid-modifying drugs in patients without established CVD. More sophisticated indication-specific pricing, coverage, and reimbursement policies, which align a price per drug indication, could help to overcome this unmet need [47, 48]. Otherwise, academic institutes could support trials for primary CV prevention.

Although the new lipid-modifying treatments in this study were proven to significantly reduce the risk of MACE, adherence to these drugs remains low [44]. Particularly impractical administration routes, side-effects, high drug prices resulting in financial toxicity, and lacking physician/patient education pose significant barriers to long-term compliance. Therefore, clinicians are eagerly awaiting trial results from lipid-modifying agents with more convenient administration routes (oral [NNC0385-0434: NCT04992065] or semi-annual [inclisiran: ORION-4] PCSK9 inhibitors), statin alternatives with fewer side effects (bempedoic acid: CLEAR Outcomes), and novel mechanisms of action (vupanorsen, volanesorsen, pelacarsen, olpasiran). More available therapeutics could permit more individualised patient care and drive down prices by increasing competition.

5 Conclusion

Icosapent ethyl in combination with statins is cost effective for primary and secondary cardiovascular prevention at an annual price of £2064 in the UK relative to statin monotherapy. Especially an aggressive therapeutic strategy targeting patients younger than 65 years with elevated triglycerides of ≥ 200 mg/dL (≥ 2.3 mmol/L) and low HDL-C levels of ≤ 35 mg/dL (≤ 0.9 mmol/L) further reduces icosapent ethyl's cost-effectiveness ratios. At list prices around £4400, PCSK9 inhibitors are not cost effective for secondary prevention. Cost effectiveness can be achieved with price discounts of − 37% to − 53% or by restricting prescription to patients with LDL-C levels beyond 100 mg/dL (2.6 mmol/L). For secondary prevention, ezetimibe and fenofibrate are low-cost generics that lower the risk of ischaemic cardiovascular events, whilst providing savings for the healthcare system.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-022-01173-3.

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest DM served as an advisor to NB Capital ApS. All other authors declare no conflicts of interest.

Author contributions Concept and design: DM, TM. Acquisition of data: DM, TM. Analysis and interpretation of data: DM, JM, TB, TM. Drafting of the manuscript: DM. Critical revision of the paper for important intellectual content: DM, JM, TB, TM. Statistical analysis: DM. Supervision: DM, JM, TB, TM.

Availability of data and materials The data underlying this study are available in the article and in its online supplementary material.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

References

1. Office for National Statistics. Leading causes of death, UK: 2001 to 2018. Registered leading causes of death by age, sex and country. 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/articles/Leadingcausesofdeathuk/2001to2018. Accessed 16 Jan 2022.
2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337.
3. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010;304:1350–7.
4. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305:2556–64.
5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
6. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097–107.
7. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
8. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11–22.
9. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371:203–12.
10. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
11. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41:111–88.
12. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1264–72.
13. Klempfner R, Erez A, Sagit B-Z, Goldenberg I, Fisman E, Kopel E, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes. 2016;9:100–8.
14. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res. 2017;120:229–43.
15. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, et al. European Society of Cardiology: cardiovascular disease statistics 2019. Eur Heart J. 2020;41:12–85.
16. Ademi Z, Ofori-Asenso R, Zomer E, Owen A, Liew D. The cost-effectiveness of icosapent ethyl in combination with statin therapy compared with statin alone for cardiovascular risk reduction: Eur J Prev Cardiol. 2021;28(8):897–904.
17. Weintraub WS, Bhatt, Zugui Z, Cheng Z, Dolman S, Boden WE, et al. Cost-effectiveness of icosapent ethyl in us reduce-it patients. J Am Coll Cardiol. 2020;75:1914–1914.
18. Gao L, Moodie M, Li S-C. The cost-effectiveness of omega-3 polyunsaturated fatty acids—the Australian healthcare perspective. Eur J Intern Med. 2019;67:70–6.
19. Ollendorf DA, McQueen RB, Campbell JD, Synnott PG, Herron-Smith S, Fazioli K, et al. Additive therapies for cardiovascular disease: effectiveness and value. Institute for Clinical and Economic Review; 2019. Available from: https://icer.org/assessment/cvd-additive-therapies-2019/. Accessed 22 Mar 2022.
20. Lachaine J, Charron JN, Gregoire JC, Hegele RA, Leiter LA. PCV55 cost-effectiveness of icosapent ethyl (IPE) for the reduction of the risk of ischemic cardiovascular events in Canada. Value Health. 2020;23:S496.
21. CADTH Canadian Drug Expert Committee Recommendation: Icosapent Ethyl (Vascepa—HLS Therapeutics Inc.): Indication: prevention of cardiovascular events in statin-treated patients. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020. Available from: http://www.ncbi.nlm.nih.gov/books/NBK566005/. Accessed 23 Jan 2022.
22. Fonarow GC, van Hout B, Villa G, Arellano J, Lindgren P. Updated cost-effectiveness analysis of evolocumab in patients with very high-risk atherosclerotic cardiovascular disease. JAMA Cardiol. 2019;4:691–5.
23. Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-effectiveness of lipid-lowering therapies for cardiovascular prevention in Germany. Cardiovasc Drugs Ther. 2022. https://doi.org/10.1007/s10557-021-07310-y.
24. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual—process and methods [PMG20]. 2020. Available from: https://www.nice.org.uk/process/pmg20/resources. Accessed 15 Jan 2022.
25. Marquina C, Zomer E, Vargas-Torres S, Zoungas S, Ofori-Asenso R, Liew D, et al. Novel treatment strategies for secondary prevention of cardiovascular disease: a systematic review of cost-effectiveness. Pharmacoeconomics. 2020;38:1095–113.
26. Danese MD, Gleeson M, Kutikova L, Griffiths RI, Azough A, Khunti K, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ Open. 2016;6: e011805.
27. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet Med J Br Diabet Assoc. 2015;32:459–66.
28. Reifsnider OS, Kansal AR, Franke J, Lee J, George JT, Brueckmann M, et al. Cost-effectiveness of empagliflozin in the UK in an EMPA-REG OUTCOME subgroup with type 2 diabetes and heart failure. ESC Heart Fail. 2020;7(6):3910–3918.
29. T. Georghiou, M. Bardsley. Exploring the cost of care at the end of life. London: Nuffield Trust Research Report. 2014. Available from: https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf. Accessed 5 Jul 2022.
30. Public Health England. Statistical commentary: End of life care profiles, February 2018 update. 2018. Available from: https://www.gov.uk/government/statistics/end-of-life-care-profiles-february-2018-update/statistical-commentary-end-of-life-care-profiles-february-2018-update. Accessed 16 Jan 2022.
31. Joint Formulary Committee. British national formulary 80. London: BMJ Publishing and the Royal Pharmaceutical Society; 2020.
32. Watkinson RE, Sutton M, Turner AJ. Ethnic inequalities in health-related quality of life among older adults in England: secondary analysis of a national cross-sectional survey. Lancet Public Health. 2021;6:e145–54.
33. Lewis EF, Li Y, Pfeffer MA, Solomon SD, Weinfurt KP, Velazquez EJ, et al. Impact of cardiovascular events on change in

quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction). JACC Heart Fail. 2014;2:159–65.
34. National Institute for Health and Care Excellence (NICE). Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: Technology appraisal guidance [TA394]. 2016. Available from: https://www.nice.org.uk/guidance/ta394/resources/evolocumab-for-treating-primary-hypercholesterolaemia-and-mixed-dyslipidaemia-82602910172869. Accessed 5 Jul 2022.
35. National Institute for Health and Care Excellence (NICE). Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: Technology appraisal guidance [TA393]. 2016. Available from: https://www.nice.org.uk/guidance/ta393/resources/alirocumab-for-treating-primary-hypercholesterolaemia-and-mixed-dyslipidaemia-82602908493253. Accessed 5 Jul 2022.
36. Bhatt DL, Briggs AH, Reed SD, Annemans L, Szarek M, Bittner VA, et al. Cost-effectiveness of alirocumab in patients with acute coronary syndromes: the ODYSSEY OUTCOMES Trial. J Am Coll Cardiol. 2020;75:2297–308.
37. Bagepally BS, Sasidharan A. Incremental net benefit of lipid-lowering therapy with PCSK9 inhibitors: a systematic review and meta-analysis of cost-utility studies. Eur J Clin Pharmacol. 2021;78(3):351–363.
38. Korman MJ, Retterstøl K, Kristiansen IS, Wisløff T. Are PCSK9 inhibitors cost effective? Pharmacoeconomics. 2018;36:1031–41.
39. Azari S, Rezapour A, Omidi N, Alipour V, Behzadifar M, Safari H, et al. Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: a systematic review. Heart Fail Rev. 2020;25:1077–88.
40. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.
41. Sarajlic P, Artiach G, Larsson SC, Bäck M. Dose-dependent risk reduction for myocardial infarction with eicosapentaenoic acid: a meta-analysis and meta-regression including the STRENGTH Trial. Cardiovasc Drugs Ther. 2021;35:1079–81.
42. Kodera S, Morita H, Kiyosue A, Ando J, Komuro I. Cost-effectiveness of statin plus eicosapentaenoic acid combination therapy for cardiovascular disease prevention in japanese patients with hypercholesterolemia—an analysis based on the Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS). Circ J Off J Jpn Circ Soc. 2018;82:1076–82.
43. Kastelein JJP, Stroes ESG. FISHing for the miracle of eicosapentaenoic acid. N Engl J Med. 2019;380:89–90.
44. Steen DL, Khan I, Ansell D, Sanchez RJ, Ray KK. Retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open. 2017;7: e013255.
45. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database Syst Rev. 2018;11:CD012502.
46. Schmidt AF, Carter J-PL, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020;10:C011748.
47. Michaeli DT, Mills M, Michaeli T, Miracolo A, Kanavos P. Initial and supplementary indication approval of new targeted cancer drugs by the FDA, EMA, Health Canada, and TGA. Invest New Drugs. 2022. https://doi.org/10.1007/s10637-022-01227-5.
48. Michaeli DT, Mills M, Kanavos P. Value and price of multi-indication cancer drugs in the USA, Germany, France, England, Canada, Australia, and Scotland. Appl Health Econ Health Policy. 2022. https://doi.org/10.1007/s40258-022-00737-w.
49. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;316:743–53.