

Aus der III. Medizinischen Klinik
der Medizinischen Fakultät Mannheim
(Direktor: Prof. Dr. med. Wolf-Karsten Hofmann)

Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention

Inauguraldissertation
zur Erlangung des medizinischen Doktorgrades
der
Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
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aus
Bad Nauheim
2024

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Partial results of this dissertation were published in:

Michaeli DT, Michaeli JC, Albers S, Boch T, Michaeli T. Established and Emerging Lipid-Lowering Drugs for Primary and Secondary Cardiovascular Prevention. *American Journal of Cardiovascular Drugs*. 2023;23(5):477-495. doi:10.1007/s40256-023-00594-5

American Journal of Cardiovascular Drugs (2023) 23:477–495
<https://doi.org/10.1007/s40256-023-00594-5>

LEADING ARTICLE



Established and Emerging Lipid-Lowering Drugs for Primary and Secondary Cardiovascular Prevention

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Accepted: 2 July 2023 / Published online: 24 July 2023
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Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention in Germany. *Cardiovascular Drugs and Therapy*. 2023 Aug;37(4):683-694. doi:10.1007/s10557-021-07310-y

Cardiovascular Drugs and Therapy
<https://doi.org/10.1007/s10557-021-07310-y>

ORIGINAL ARTICLE



Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention in Germany

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Accepted: 22 December 2021
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Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Icosapent Ethyl, Evolocumab, Alirocumab, Ezetimibe, or Fenofibrate in Combination with Statins Compared to Statin Monotherapy. *Clinical Drug Investigation*. 2022;42(8):643-656. doi:10.1007/s40261-022-01173-3

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

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Accepted: 16 June 2022 / Published online: 11 July 2022
© The Author(s) 2022

Partial results of this dissertation were presented at the European Society of Cardiology Conference 2022 in Barcelona, Spain:

Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Icosapent Ethyl for Primary and Secondary Cardiovascular Prevention in the UK. *European Heart Journal*. 2022;43(Supplement 2). doi:10.1093/eurheartj/ehac544.2845

JOURNAL ARTICLE

Cost-effectiveness of icosapent ethyl for primary and secondary cardiovascular prevention in the UK FREE

D T Michaeli, J C Michaeli, T Boch, T Michaeli

European Heart Journal, Volume 43, Issue Supplement_2, October 2022, ehac544.2845, <https://doi.org/10.1093/eurheartj/ehac544.2845>

Published: 03 October 2022

Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Cholesterol-Lowering Drugs for Secondary Cardiovascular Prevention in the UK: Ezetimibe, Evolocumab, and Alirocumab. *European Heart Journal*. 2022;43(Supplement 2). doi:10.1093/eurheartj/ehac544.2367

JOURNAL ARTICLE

Cost-effectiveness of cholesterol-lowering drugs for secondary cardiovascular prevention in the UK: ezetimibe, evolocumab, and alirocumab FREE

D T Michaeli, J C Michaeli, T Boch, T Michaeli

European Heart Journal, Volume 43, Issue Supplement_2, October 2022, ehac544.2367, <https://doi.org/10.1093/eurheartj/ehac544.2367>

Published: 03 October 2022

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1 Abbreviations

ACS	Acute coronary syndrome
ANGPTL3	Angiopoietin-like 3
ApoA-I	Apolipoprotein A-I
ApoB-100	Apolipoprotein B-100
ApoC-III	Apolipoprotein C-III
ATP	Adenosine triphosphate
CADTH	Canadian Agency for Drugs & Technologies in Health
CVD	Cardiovascular diseases
CVOT	Cardiovascular outcome trial
DALY	Disability-adjusted life year
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
EMA	European Medicines Agency
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
FCS	Familial chylomicronemia syndrome
FDA	US Food and Drug Administration
GBD	Global Burden of Diseases
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HoFH	Homozygous familial hypercholesterolemia
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
ICER	Incremental cost-effectiveness ratio
IQWiG	Institute for Quality and Efficiency in Health Care
LDL-C	Low-density lipoprotein cholesterol
LY	Life year
Lp(a)	Lipoprotein (a)
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MoA	Mechanism of action
mRNA	Messenger ribonucleic acid
MTG	Microsomal triglyceride transfer protein
NHS	National Health Service
NNT	Number needed to treat
NPC1L1	Niemann-Pick C1-Like 1
PCSK9	Proprotein convertase subtilisin-kexin type 9
PPAR α	Peroxisome proliferator-activated receptor alpha
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
siRNA	Small interfering ribonucleic acid
VLDL	Very-low-density lipoprotein
WTP	Willingness-to-pay

2 Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide.¹ In 2019, the Global Burden of Diseases Study (GBD) estimated that a total of 18.6 million (32.8%) people died from CVD – compared to the 10.1 million (17.8%) that died from neoplasms (Figure 1).² Among CVD, most deaths are attributable to ischemic heart diseases (16.2%), strokes (11.6%), and hypertensive heart diseases (2.0%).

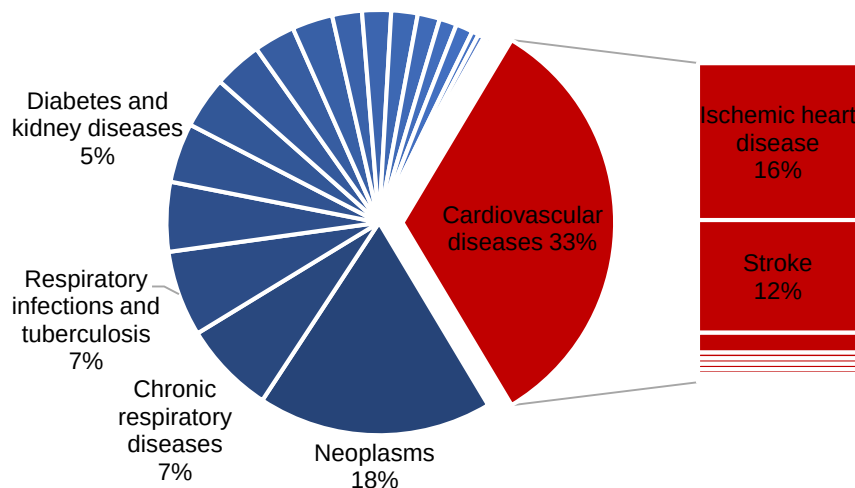


Figure 1: Causes of death in 2019 (worldwide)

The chart presents the leading causes of death worldwide. Causes for cardiovascular death are illustrated in red and other causes in blue. Data were obtained from the GBD study (2019).² GBD Global Burden of Diseases.

Globally, the incidence and prevalence rates of CVD are on the rise; ultimately resulting in a continued increase in the burden that is inflicted upon patients and healthcare systems.^{3–5} From 1990 to 2019, the global annual incidence rate of CVD (per 100,000) rose from 585 to 717 (+22%), and the prevalence rose from 5,069 to 6,762 (+33.4%).² The absolute prevalence of CVD remains highest in the Western world with an annual rate (per 100,000) of 11,647 and 12,095 in the EU and the US, respectively. Nonetheless, Figure 2 shows that particularly in Asia, e.g. China (+99.7%), Thailand (96.2%), Korea (75.9%), India (54.1%), and the Arabic world (Middle East and North Africa), e.g. Syria (+88.0%), Tunisia (+85.9%), United Arab Emirates (+76.9%), CVD are surging.

Metabolic, behavioural, environmental, and occupational risk factors adversely affect the incidence and progression of CVD.^{1,4–7} High systolic blood pressure, dietary risks, and elevated low-density lipoprotein cholesterol (LDL-C) levels count among the top three cardiovascular risk factors; each attributable for 25.0%, 17.2%, and 11.0% of CVD deaths, respectively (Table 1).² Despite the widespread availability of low-cost statins, the majority of dyslipidaemia patients do not attain adequate LDL-C levels by existing lifestyle modifications and pharmacological treatment strategies.^{8–12} The DA VINCI study found that out of 5,888 dyslipidaemia patients that were enrolled in 18 European countries, only 33% achieved their risk-based LDL-C goal recommended in ESC 2019 guidelines.¹³ These results were consistent across European countries.^{14–16} Accordingly, an Australian study of 61,407 patients reported that only 36% achieved their recommended LDL-C levels.¹⁷ Similarly, Klimchak et al. use claims data from 44

million US inhabitants to estimate that only 36% of high-risk patients with atherosclerotic CVD attain the recommended LDL-C level of <70 mg/dL.¹⁸ There are several reasons why the majority of patients do not sufficiently reach LDL-C levels. First, ESC and AHA/ACC/multi-society guidelines have recently pursued stricter LDL-C reductions according to the principle: “the lower, the better”.^{19–21} For example, the recommended LDL-C level for very-high risk patients has been lowered from <70 to <55 mg/dL. Second, patients may be reluctant to pursue lower LDL-C levels with lifestyle modifications and regular pharmaceutical therapy in the absence of short-term consequences. Third, high prices for new treatments, such as PCSK9 inhibitors, have been identified as a barrier to swift coverage and reimbursement by insurers.^{22–25} Finally, there may simply not be a sufficient number of add-on and alternative therapies to statins given that approximately 9.1% of patients are intolerant to statins.²⁶ As a consequence, multiple authors have concluded that there is a significant unmet medical need for dyslipidaemia patients to reduce blood lipid levels to prevent the incidence of adverse cardiovascular events.^{27–31}

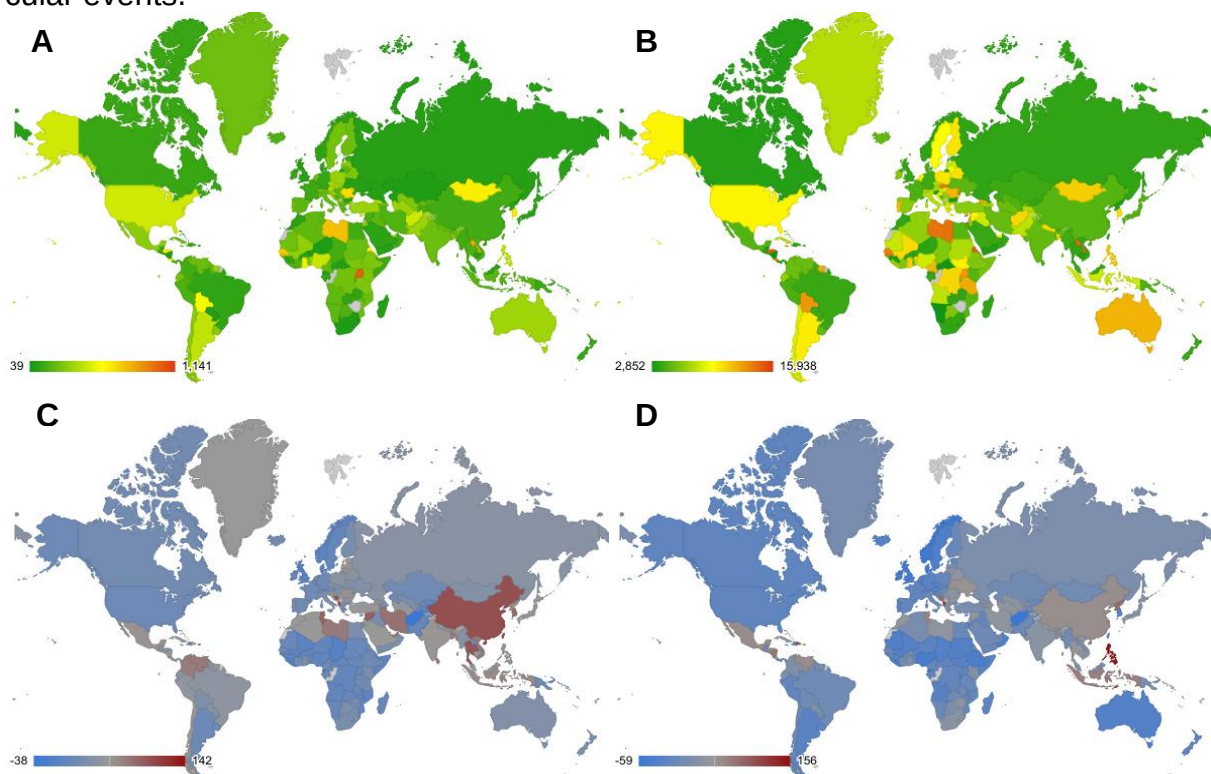


Figure 2: Global change in cardiovascular disease epidemiology from 1990 to 2019

The annual (A) death and (B) prevalence rate per 100,000 inhabitants is presented for 2019. Colours illustrate high (red), medium (yellow), and low (green) rates relative to other nations. Each region's change in (C) death and (D) prevalence rates per 100,000 inhabitants is displayed from 1990 to 2019. Colours visualize increases (red), constant (grey), and decreases (blue) in rates. Underlying data are attached in the Appendix, including data for DALYs and incidence rates. Data were obtained from the GBD study (2019).² DALY disability-adjusted life year, GBD Global Burden of Diseases.

Further, diabetes mellitus, a high body-mass index (BMI), tobacco, physical inactivity, and alcohol consumption count among the most important modifiable risk factors. Collectively, these modifiable risk factors account for 86.0% of CVD deaths (metabolic factors: 58.0% and behavioural factors: 27.9%).²

Risk factor	Rank			Attributable deaths		
	1990	2019	Change	1990	2019	Change
Individual						
High systolic blood pressure	1	1	→ 0	25.1%	25.0%	→ -0.1%
Dietary risks	2	2	→ 0	18.8%	17.2%	↓ -1.6%
High LDL cholesterol	3	3	→ 0	11.7%	11.0%	↓ -0.6%
High fasting plasma glucose	6	4	↑ 2	6.8%	9.5%	↑ 2.6%
Air pollution	4	5	↓ -1	10.1%	8.9%	↓ -1.2%
High body-mass index	7	6	↑ 1	6.3%	8.1%	↑ 1.8%
Tobacco	5	7	↓ -2	9.9%	8.0%	↓ -1.9%
Kidney dysfunction	8	8	→ 0	3.8%	4.4%	→ 0.6%
Non-optimal temperature	9	9	→ 0	3.2%	3.0%	→ -0.2%
Other environmental risks	10	10	→ 0	2.0%	2.1%	→ 0.2%
Low physical activity	11	11	→ 0	1.4%	1.6%	→ 0.2%
Alcohol use	12	12	→ 0	0.9%	1.1%	→ 0.1%
Category						
Metabolic risks	1	1	↑ 0	53.6%	58.0%	↑ 4.4%
Behavioural risks	2	2	↑ 0	31.1%	27.9%	↓ -3.1%
Environmental/occupational risks	3	3	↑ 0	15.3%	14.0%	↓ -1.3%

Table 1: Risk factors for cardiovascular diseases

Twelve individual risk factors for CVD are presented. Factors were ranked in 1990 and 2019 according to attributable deaths. The percentage of deaths attributable to individual risk factors is presented for 1990 and 2019. Risks were further categorized according to metabolic (green), behavioural (blue), and environmental/occupational (yellow) factors. Data were obtained from the GBD study (2019).² CVD cardiovascular diseases, GBD Global Burden of Diseases, LDL low-density lipoprotein.

In summary, CVD is the major cause of death worldwide with rising incidence rates. Therefore, the reduction of cardiovascular risk factors and thereby the prevention of major cardiovascular events lies not only at the heart of cardiologists' and family physicians' clinical practice but has also emerged as an overarching public health strategy. Governments around the globe are designing policies to reduce the rising socio-economic burden of CVD.^{32–38} Public health and pharmacologic efforts particularly target patients with arterial hypertension, dyslipidaemia, obesity, and diabetes mellitus, which are the leading metabolic risk factors for atherosclerosis and resulting chronic CVD. This dissertation focuses on dyslipidaemia and lipid-lowering drugs. First, strategies to prevent CVD among dyslipidaemia patients are described with a review of current and emerging pharmacological treatment options. Thereafter, the costs arising from CVD are discussed, particularly focusing on established methodologies to evaluate the costs and benefits of a new treatment for cardiovascular prevention. The introduction section concludes by deriving this dissertation's objectives and highlighting this work's relevance for clinical practice.

2.1 Cardiovascular prevention in dyslipidaemia patients

For all dyslipidaemia patients with a substantial risk of experiencing cardiovascular events, the ESC recommends lifestyle modifications including an improved diet, consisting of fewer trans fats, saturated fats, and more fibers, and more physical activity leading to a reduction in body weight and BMI.²⁰ Furthermore, it is highly recommended to quit smoking, alcohol, and any other harmful drugs. Patients refractory to this lifestyle modification may receive pharmacological treatment. This section provides an

overview of established and emerging pharmaceutical therapies to prevent cardiovascular events in patients with dyslipidaemia.

2.1.1 Established pharmaceutical therapies

ESC guidelines entail a list of pharmaceutical interventions that may be used in patients with dyslipidaemia to lower blood lipids and ultimately the risk of adverse cardiovascular events. This section briefly reviews the most commonly used lipid-lowering drugs regarding their mechanism of action (MoA), effects on blood lipids, reduction of cardiovascular morbidity and mortality, and side effects (Table 2).

Name	MoA	Type	RoA	LDL-C	TG	MACE
Low/Medium-intensity statins	HMG-CoA-reductase inhibition, pleiotropic		1x daily, p.o.	-30%	-20%	-22%
High-intensity statins	HMG-CoA inhibition, pleiotropic		1x daily, p.o.	-50%	-40%	-15%
Ezetimibe	NPC1L1 inhibition		1x daily, p.o.	-24%	-12%	-6%
Evolocumab	PCSK9 inhibition		Biweekly/ monthly, s.c.	-60%	-26%	-15%
Alirocumab	PCSK9 inhibition		Biweekly/ monthly, s.c.	-60%	-26%	-15%
Fibrates	PPAR α activation		1x daily, p.o.	-20%	-50%	-10%
Icosapent ethyl	TG lowering, pleiotropic		2x daily, p.o.	-6%	-20%	-25%

Table 2: Established lipid-lowering therapies for cardiovascular prevention

LDL-C, TG, and MACE reductions for ezetimibe, evolocumab, alirocumab, fibrates, and icosapent ethyl are presented for combination therapy with statins. Data sources as referenced in the accompanying text passages. *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A, *i.v.* intravenous, *LDL-C* low-density lipoprotein cholesterol, *MACE* major adverse cardiovascular events, *MoA* mechanism of action, *NPC1L1* Nieman pick C1 like 1 protein, *PCSK9* proprotein convertase subtilisin-kexin type 9, *p.o.* perioral, *PPAR- α* peroxisome proliferator receptor alpha, *RoA* route of administration, *s.c.* subcutaneous, *TG* triglyceride.

Statins

Statins reduce the internal synthesis of cholesterol by competitive inhibition of the rate-limiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.²⁰ The reduced internal synthesis of cholesterol results in an increased surface expression of LDL-C receptors, which then increases the uptake of LDL-C. Ultimately, this results in lower serum LDL-C, ApoB-100, and triglyceride levels. Given the competitive inhibition of HMG-CoA, statins' dose-dependent efficacy is used in clinical practice to escalate treatment from low-/medium-intensity to high-intensity statin treatment for at-risk patients. Low-/medium-intensity statins reduce LDL-C by -30% to -50% and triglycerides by -20%, whilst high-intensity statins reduce LDL-C by more than -50% and triglycerides by up to -40%.^{20,39} Statins also elevate high-density lipoprotein cholesterol (HDL-C) in a dose-dependent manner by up to +10%.⁴⁰ Studies reported no or only a minor

increase in lipoprotein (a) (Lp(a)) levels among patients treated with statins.^{41,42} Beyond the modification of blood lipid levels, in-vitro and in-vivo studies showed that statins exert beneficial cardioprotective pleiotropic effects.^{43,44} These “include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques.”⁴³ However, the significance of these pleiotropic effects in clinical practice remains debated.⁴⁵

Statins’ relevance in cardiovascular prevention is supported by multiple meta-analyses across several patient subgroups.^{46–58} According to an analysis of 170,000 patients, a 38.67 mg/dl (1 mmol/l) reduction in LDL-C was associated with a -22% (95%CI: -20 to -24, $p < 0.0001$) decreased risk in major adverse cardiovascular events (MACE),⁴⁶ thereby confirming LDL-C as a valid surrogate parameter for the clinical endpoints MACE and cardiovascular death. Overall, low-/moderate-intensive statin therapy reduces the risk of MACE by -22% (95%CI: -19 to -24, $p < 0.0001$).⁴⁶ Further intensifying statin therapy provides an additional MACE risk reduction of -15% (95%CI: -11 to -18, $p < 0.0001$).⁴⁶ Results were consistent across primary and secondary prevention cohorts.^{48,49,56,57,59} In patients with low risk of CVD ($< 10\%$ risk), statin therapy reduced the risk of major vascular events (RR: 0.79, 95%CI: 0.77 to 0.81 per 1.0 mmol/L reduction in LDL-C) irrespective of previous vascular diseases.⁴⁸ Statin therapy reduced the risk of all-cause mortality by 9% per 1.0 mmol/L LDL-C reduction.

The clinically most significant adverse effects of statin therapy are muscle-associated symptoms including myopathy (11 per 100,000 patient-years) up to rhabdomyolysis (3 per 100,000 patient-years),⁶⁰ an elevation of liver enzymes, hyperglycaemia⁶¹, new onset of diabetes mellitus type 2,⁶² and proteinuria. Evidence for an increased risk of haemorrhagic stroke remains inconclusive.^{46,62,63} As statins are metabolized through the hepatic pathway, inhibitors and inducers of the CYP system, e.g. anti-infectives, calcium antagonists, cyclosporine, and grapefruit juice, may cause drug-drug interactions which impact their bioavailability; ultimately leading to the aggravation of side effects or limited therapeutic efficacy. A recent meta-analysis of 176 studies with a total of 4.1 million patients found that 9.1% of patients are intolerant to statins.²⁶ Age, female gender, Asian and Black race, obesity, diabetes mellitus, hypothyroidism, chronic liver disease, renal failure, antiarrhythmic drugs, calcium channel blockers, alcohol consumption, and higher statin dose were associated with a greater risk of statin intolerance.²⁶

Albeit statins are the first-line therapeutic option to lower blood lipids in dyslipidaemia patients, e.g. those with hypercholesterinaemia or hypertriglyceridemia, many patients’ blood lipids remain above the risk-stratified target levels defined by ESC guidelines. To reduce the risk of adverse cardiovascular events among these at-risk patients, new pharmacological treatment options have been developed over the past two decades. New treatments may be prescribed adjuvant to moderate-/high-intensity statins or as monotherapy for patients intolerant to statins.

Ezetimibe

Ezetimibe selectively inhibits the absorption of cholesterol in the small intestine (by interfering with the Nieman pick C1-like 1 protein [NPC1L1]) without modifying the uptake of other nutrients and vitamins.^{64,65} A genetic sequencing study involving more than 90,000 patients found significantly lower LDL-C levels and a lower risk of coronary

heart disease among patients with NPC1L1 mutations.⁶⁶ Compared to statin monotherapy, a combination of ezetimibe and statins reduces LDL-C by -24%, ApoB-100 by -14%, triglycerides by -12%, and high-sensitivity C-reactive protein (hsCRP) by -13%, whilst maintaining HDL-C levels.^{67–69} The randomized controlled double-blind Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) enrolling 18,144 patients after acute coronary syndrome with a follow-up of 6 years found that ezetimibe added to simvastatin compared to simvastatin monotherapy significantly reduced the risk of MACE by -6% (95%CI: -1 to -11, $p=0.016$). Although the earlier ENHANCE trial could not confirm that addition of ezetimibe to statins significantly reduces intima-media thickness in patients with familial hypercholesterolemia, the SHARP and SEAS trials highlight ezetimibe's role in the prevention of ischaemic cardiovascular events.^{70–73} Ezetimibe's safety and efficacy have been confirmed in multiple meta-analyses.^{69,74–78}

The Japanese EWTOPIA 75 trial investigated ezetimibe as monotherapy for primary cardiovascular prevention in patients 75 years or older. 3,796 patients were randomly assigned to ezetimibe (10 mg daily) versus usual care. After a median follow-up of 4.1 years, ezetimibe reduced the incidence of MACE by -34% (HR: 0.66, 95% CI: 0.50 to 0.86, $p=0.002$).⁷⁹

Compared to statin monotherapy, adjuvant ezetimibe was not found to increase the occurrence of side effects or treatment discontinuation.

PCSK9 inhibitors

Evolocumab and alirocumab are monoclonal antibodies that inhibit the proprotein convertase subtilisin-kexin type 9 (PCSK9). These antibodies reduce the concentration of PCSK9 plasma levels, which results in an increased expression of LDL-C receptors and thereby reduced LDL-C levels. Consequently, genetic studies found significantly lower LDL-C levels and fewer cardiovascular events in patients with PCSK9 loss-of-function mutations compared to control.^{80–82} Treatment with PCSK9 inhibitors reduces LDL-C by approx. -60%.^{83–87} PCSK9 inhibitors also lower triglycerides and Lp(a), whilst increasing ApoA-I. Coherent with the LDL-C reduction, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) trials found that PCSK9 inhibitors significantly reduce the risk of MACE by -15% in patients with prior acute cardiovascular syndrome. These double-blinded trials randomized 27,564/18,924 patients to receive evolocumab/alirocumab or placebo in addition to statins with a follow-up period of 2.2/2.8 years. The cardioprotective effects of PCSK9 inhibitors were subsequently confirmed in other clinical trials and meta-analyses.^{88–93}

Schmidt et al.'s meta-analysis of PCSK9 inhibitors includes trials with primary and secondary prevention cohorts.⁸⁸ Trials either include patients with established CVD or at high CVD risk. However, outcome data is infrequently reported for the primary and secondary prevention cohorts, separately. Data from the GLAGOV, ODYSSEY COMBO I, and ODYSSEY LONG TERM trials show a greater efficacy of PCSK9 inhibitors in patients with prior CVD (or myocardial infarction) in terms of LDL-C and percent atheroma volume.^{94–96}

Subcutaneous application of the monoclonal antibodies results in local injection-site reactions. PCSK9 inhibitors were also discussed to induce the expression of auto-antibodies and increase the risk of diabetes mellitus.^{97,98}

Fibrates

Fibrates, such as fenofibrate, bezafibrate, and gemfibrozil, activate the peroxisome proliferator receptor alpha (PPAR- α) and thereby reduce blood lipid levels. Fibrates reduce concentrations of triglycerides by approximately -50% and LDL-C by -20%, whilst increasing HDL-C by up to +20% depending on the fibrate class.²⁰ Treatment with fibrates is associated with an increased risk of gastrointestinal pain, skin rashes, myopathy, and liver enzyme elevation.²⁰ Evidence supporting the prescription of fibrates for cardiovascular prevention remains debated. The ACCORD, LEADER, and VA-COOP trials could not confirm that fibrates reduce the incidence of MACE at a 5% significance level, whilst a significant MACE reduction was observed in the FIELD and VA-HIT trials.^{99–102} A meta-analysis pooling outcomes from these trials found that fibrates significantly reduce the risk of MACE by -10% (95%CI: -0 to -18, $p=0.048$).^{102,103} The same analysis also finds fibrates to reduce the incidence of coronary events, yet not death. Consequently, fibrates' role in cardiovascular prevention remains debated. ESC and AHA/ACC/multi-society guidelines recommend fibrates for dyslipidaemia patients with elevated triglycerides despite statin treatment. Yet, their role in cardiovascular prevention and triglyceride reduction is projected to diminish following icosapent ethyl's approval.

Omega-3 fatty acids

Since observational studies suggested high omega-3 fatty acid levels are associated with a lower risk of cardiovascular events and death, researchers evaluated these acids in randomized controlled trials (RCTs). Particular interest surrounded the “fish oils” docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and most recently docosapentaenoic acid (DPA). Although several large-scale RCTs evaluated these omega-3 fatty acids, the public and scientific community remains puzzled about their differential outcomes. The STRENGTH, VITAL, ASCEND, ORIGIN, OMEGA, ALPHA-OMEGA, GISSI-HF, and GISSI-P trials randomized patients to receive either a combination of EPA and DHA or placebo; yet only the GISSI trials noted a statistically significant effect on cardiovascular events and mortality.^{104–111} In contrast, patients receiving only high-dose EPA in the REDUCE-IT and JELIS trials were at -25% (95%CI: -17 to -32, $p<0.001$) and -19% (95%CI: -5 to -31, $p=0.011$) lower risk for MACE, respectively.^{112,113}

These differential treatment effects could be subject to the administered omega-3 fatty acid, dosing regimen, comparator, and studied patient population. In-vitro and in-vivo experimental studies highlight EPA's and DHA's distinct effects on inflammation, cellular membranes, platelets, and triglycerides which could result in the observed differential MACE outcomes.^{114,115} Albeit the exact MoA is unknown, scientists hypothesize that EPA exerts pleiotropic cardiovascular effects beyond lowering triglycerides: anti-inflammatory, anti-thrombotic, membrane stabilizing, plaque stabilizing, anti-arrhythmic, and anti-hypertensive.^{113,114,116,117} Systematic reviews of the aforementioned studies with meta-analyses and -regressions show a dose-dependent association between omega-3 fatty acids' titration and cardiovascular events.^{112,114,117–119} The REDUCE-IT and JELIS trials randomized patients to receive 4 g and 1.8 g of highly purified EPA, whilst the EPA dosage was significantly lower in the other trials. Although there has been a significant public debate surrounding the comparator used in the REDUCE-IT

trial (mineral oil),^{120,121} experts in both regulatory agencies in the US and the EU – from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – approved highly purified EPA, icosapent ethyl, for cardiovascular prevention in dyslipidaemia patients. It is estimated that the inappropriate use of mineral oil as a comparator may have overestimated the MACE outcome by up to 3%.¹²² The resulting net MACE reduction of -22% then closely resembles the -19% MACE reduction observed in the JELIS trial.

Notably, the REDUCE-IT trial enrolled 29% of patients without CVD (primary prevention) and 71% of patients with established CVD (secondary prevention).¹¹³ Subgroup analyses showed a non-significantly greater MACE reduction in the secondary prevention (HR: 0.73, 95%CI: 0.65 to 0.81) than the primary prevention cohort (HR: 0.88, 95%CI: 0.70 to 1.10, $p=0.14$). A post-hoc analysis of the REDUCE-IT trial confirmed icosapent ethyl's efficacy among patients with prior myocardial infarction (MACE HR: 0.74, 95%CI: 0.65 to 0.85, $p<0.001$).¹²³ Similarly, the JELIS trial, which predominantly included patients without established CVD, demonstrated a consistent efficacy of EPA in the primary (HR: 0.82, 95%CI: 0.63 to 1.06, $p=0.132$) and secondary prevention cohorts (HR: 0.81, 95%CI: 0.657-0.998, $p=0.048$).¹¹² Consequently, recent economic analyses found icosapent ethyl could be a cost-effective treatment, particularly for secondary cardiovascular prevention, in the US, Germany, the UK, Canada, Australia, and Japan.^{23,24,124–129}

Treatment with EPA was observed to be associated with a higher incidence of arterial fibrillation, serious bleeding events (e.g. haemorrhagic strokes), and peripheral oedema; yet a lower incidence of diarrhoea, gastrointestinal pain, and anaemia than monotherapy with statins.^{113,114}

Other drugs

Several other pharmacological treatments are/were used to treat patients with dyslipidaemia, such as bile acid sequestrants and niacin. Bile acid sequestrants, such as cholestyramine, colestesvelam, and colestipol, bind to intestinal cholesterol and thereby inhibit its absorption in the small intestine, effectively removing it from the enterohepatic cholesterol circulation.²⁰ Although bile acid sequestrants are associated with a significant reduction in LDL-C and MACE, clinical trials supporting their efficacy were conducted before the introduction of statins, ezetimibe, PCSK9 inhibitors, and icosapent ethyl.¹³⁰ In the EU, treatment with niacin was stopped after the AIM-HIGH and HPS2-THRIVE trials showed no improvement in MACE, yet an increased occurrence of undesirable side effects.^{131,132}

2.1.2 Emerging pharmaceutical therapies

Recently, several novel pharmaceutical therapies with innovative MoA have been approved by the FDA and/or EMA to treat patients with dyslipidaemia. Many of these are currently investigated in cardiovascular outcome trials (CVOT). An even greater number of therapeutics are currently under clinical development. If successful, these novel pharmaceutical therapies could soon be approved and transform the management of patients with dyslipidaemia. This section reviews these emerging pharmaceutical therapies regarding their MoA, first safety and efficacy results, and ongoing clinical trials (Table 3).

Name	MoA	Drug Type	Drug Class	RoA	Ended Trials	Ongoing Trials	Phase
Bempedoic acid	ATP-citrate lyase inhibition		small-molecule	1x daily, p.o.	CLEAR trials	-	P0 → P1 → P2 → P3 → FDA → CVOT
Inclisiran	PCSK9 inhibition		siRNA	semi-annual, s.c.	ORION trials	ORION-4	P0 → P1 → P2 → P3 → FDA → CVOT
Evinacumab	ANGPTL3		monoclonal antibody	1x monthly, i.v.	ELIPSE HoFH	Pediatric HeFH, sHTG	P0 → P1 → P2 → P3 → FDA → Trials
Lomitapide	MTP inhibition		small-molecule	1x daily, p.o.	HoFH	Pediatric and pregnant patients	P0 → P1 → P2 → P3 → FDA → Trials
Mipomersen	ApoB-100 inhibition		antisense oligo-nucleotide	1x weekly, s.c.	HoFH	Long-term safety and efficacy	P0 → P1 → P2 → P3 → FDA
Volanesorsen	ApoC-III degradation		antisense oligo-nucleotide	weekly, s.c.	FCS, HTG	-	P0 → P1 → P2 → P3 → FDA
Pemafibrate	Selective PPARα modulator		small-molecule	2x daily, p.o.	Phase 1-3, PROMINENT	-	P0 → P1 → P2 → P3
Pelacarsen	Lp(a) lowering		antisense oligo-nucleotide	monthly, s.c.	Phase 2 dose finding	HORIZON	P0 → P1 → P2 → P3
DPA + EPA	TG lowering		small-molecule	2x daily, p.o.	ENHANCE-IT	-	P0 → P1 → P2
Olezarsen	ApoC-III degradation		antisense oligo-nucleotide	weekly, s.c.	Phase 1	sHTG, FCS	P0 → P1 → P2 → P3
NNC0385-0434 A	PCSK9 inhibition		^a	1x daily, p.o.	Phase 1	Phase 2 dose finding	P0 → P1 → P2
Olpasiran	Lp(a) inhibition		siRNA	12-weekly, s.c.	Phase 1	Phase 2 dose finding	P0 → P1 → P2

Table 3: Emerging pharmaceutical therapies for the treatment of dyslipidemia

Drug types were categorized and illustrated as small molecules (capsule), antibodies (syringe), and gene therapeutics (double-stranded DNA helix). Data sources as referenced in the accompanying text passages. ^a The drug class could not be identified for the compound NNC0385-0434 A. *ANGPTL3* angiotensin-like 3, *ApoB-100* apolipoprotein B-100, *ApoC-III* Apolipoprotein C-III, *ATP* adenosine triphosphate, *CVOT* cardiovascular outcome trial, *FCS* familial chylomicronemia syndrome, *FDA* US Food and Drug Administration Approval, *HeFH* heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *HTG* hypertriglyceridemia, *i.v.* intravenous, *Lp(a)* lipoprotein (a), *MoA* mechanism of action, *MTP* microsomal triglyceride transfer protein, *P0* pre-clinic, *P1* phase 1, *P2* phase 2, *P3* phase 3, *PCSK9* proprotein convertase subtilisin-kexin type 9, *PPAR-α* peroxisome proliferator receptor alpha, *p.o.* peroral, *RoA* route of administration, *s.c.* subcutaneous, *sHTG* severe hypertriglyceridemia, *siRNA* small interfering ribonucleic acid.

Bempedoic acid

Bempedoic acid inhibits the adenosine triphosphate (ATP)-citrate lyase and thereby cholesterol biosynthesis.¹³³ The ATP-citrate lyase enzyme specifically catalyses the synthesis of Acetyl-CoA, which is an underlying substrate to synthesize HMG-CoA. Although both statins and bempedoic acid inhibit cholesterol biosynthesis, bempedoic acid inhibits an enzyme that is located upstream of the HMG-CoA-reductase. Furthermore, bempedoic acid is a prodrug that is activated by the SLC27A2 enzyme which is not present in muscle cells. In contrast to statins, a lower incidence of myopathy, rhabdomyolysis, or other muscle-related side effects were observed in patients receiving bempedoic acid.¹³⁴ The most common side effects are increased uric acid levels and gout.¹³⁵ Therefore, bempedoic acid has been an eagerly awaited pharmacological alternative to reduce LDL-C levels among statin-intolerant patients.

Bempedoic acid's safety and efficacy in statin-intolerant patients have been evaluated across the family of phase 3 CLEAR trials.^{134,136–138}

- The CLEAR Tranquillity trial evaluated bempedoic acid compared to placebo in 269 patients receiving ezetimibe as background therapy.¹³⁹ Relative to placebo, bempedoic acid reduced LDL-C by -29%, non-HDL-C by -24%, total cholesterol by -18%, ApoB-100 by -19%, and hsCRP by -31%.
- The CLEAR Serenity trial randomized 345 statin-intolerant patients with hypercholesterolemia to receive bempedoic acid or placebo.¹³⁴ Bempedoic acid lowered LDL-C by -21%, non-HDL-C by -18%, total cholesterol by -15%, ApoB-100 by -15%, and hsCRP by -24%.
- The CLEAR Wisdom trial randomized 779 patients with atherosclerosis or heterozygous familial hypercholesterolemia (HeFH) to receive bempedoic acid or placebo.¹³⁶ Bempedoic acid reduced LDL-C by -17%, non-HDL by -13%, total cholesterol by -11%, ApoB-100 by -13%, and hsCRP by -9% compared to placebo.
- The CLEAR Harmony trial assessed bempedoic acid's safety and efficacy in 2,230 statin-treated patients with atherosclerosis or HeFH compared to placebo.¹³⁷ Relative to placebo, bempedoic acid reduced LDL-C by -16%, non-HDL-C by -13%, total cholesterol by -11%, ApoB-100 by -12%, and hsCRP by -22%. The incidence of adverse events was similar across both interventional groups, yet a higher percentage discontinued treatment with bempedoic acid than placebo (10.9% vs. 7.1%). Gout was more frequently observed among patients treated with bempedoic acid (1.2% vs. 0.3%).
- The CLEAR Outcomes trial randomized 13,970 patients with established or high risk for CVD, intolerance to statins, and LDL-C level ≥ 100 mg/dL to receive bempedoic acid (180 mg daily) or placebo.¹³⁸ Bempedoic acid reduced the risk of MACE by -13% (HR: 0.87, 95% CI: 0.79 to 0.96, $p=0.004$) and resulted in a -21.1% greater reduction in LDL-C levels compared to placebo.¹⁴⁰ A higher frequency of gout (3.1% vs. 2.1%) and cholelithiasis (2.2% vs. 1.2%) was observed bempedoic acid than placebo.¹⁴⁰

Based on these clinical trials, bempedoic acid has been approved to lower LDL-C in patients with HeFH or established atherosclerotic cardiovascular disease by the FDA and for primary hypercholesterolemia or mixed dyslipidaemia by the EMA. Even though data for primary CVD prevention is missing, the International Lipid Expert Panel concludes that bempedoic acid's "favourable effects on plasma glucose and inflammatory markers make this drug a rational choice in the patient-centred care of specific groups of primary prevention."¹⁴¹

Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) inhibitor of the PCSK9 biosynthesis. Although the underlying MoA is similar to evolocumab and alirocumab, the novel siRNA technology permits an infrequent subcutaneous administration (initially 284 mg for two doses three months apart and 284 mg every 6 months thereafter) with potentially fewer injection-site reactions and improved patient adherence. Inclisiran's efficacy was and is evaluated across the family of ORION trials in patients receiving maximum tolerable statins and other lipid-lowering agents:^{142–146}

- The phase 3 ORION-10 and ORION-11 trials evaluated inclisiran compared to placebo across a total of 1,561 and 1,617 patients with atherosclerosis or an atherosclerotic CVD risk-equivalent, respectively.¹⁴⁴ Compared to placebo, inclisiran reduced LDL-C levels by -52% and -50%, respectively.

- These results were confirmed in the phase 3 ORION-9 trial which showed a -48% LDL-C reduction of inclisiran relative to placebo among 482 patients with HeFH.¹⁴⁵
- The ORION-2 pilot trial showed inclisiran could also be effective for patients with homozygous familial hypercholesterinaemia (HoFH).¹⁴⁶ Based on these results, a phase 3 study involving 56 patients with HoFH has been initiated (ORION-5).¹⁴²
- Results of the ORION-9, ORION-10, and ORION-11 trials were consistent in pooled patient- and trial-level meta-analyses.^{147,148} Across all three trials, LDL-C reductions amounted to -51%. Except for injection-site rejections, patients were not at an increased risk for any adverse events. In contrast to the other PCSK9 inhibitors, inclisiran does not induce the expression of auto-antibodies according to results from the ORION-1 trial.¹⁴⁹

Inclisiran has been approved to lower LDL-C in patients with HeFH or clinical atherosclerotic cardiovascular disease by the FDA and in patients with primary hypercholesterolemia or mixed dyslipidaemia by the EMA. The CVOT enrolling a total of 15,000 (ORION-4) is expected to be completed by July 2026.¹⁴³

Evinacumab

Evinacumab is a monoclonal antibody inhibiting angiopoietin-like 3 (ANGPTL3). ANGPTL3 inhibits the lipoprotein lipase, which results in increased blood lipid levels.^{150–152} Consequently, ANGPTL3 loss-of-function mutations result in lower triglycerides, LDL-C, and a -41% decreased risk of coronary heart diseases, despite reduced HDL-C levels.^{153,154} In contrast to other pharmacological treatments, evinacumab's MoA is therefore independent of the LDL-C receptor;^{150,155} providing new options for more synergistic combination treatments.

After evinacumab's proof-of-concept was established in a single-group phase 2 trial,¹⁵⁶ the phase 3 ELIPSE trial was conducted.¹⁵⁷ Sixty-five patients with HoFH were randomized to evinacumab (15 mg per kilogram body weight intravenous) or placebo every 4 weeks. Evinacumab lowered LDL-C by -49% compared to placebo without a significant increase in adverse events. Evinacumab also significantly reduced ApoB-100 by -37%, non-HDL by -52%, total cholesterol by -48%, triglycerides by -50%, and ApoC-III by -90%. Another phase 2 trial studied evinacumab in 272 patients with refractory hypercholesterinaemia (either HeFH or established atherosclerosis). At a dose of 450 mg per week, evinacumab reduced LDL-C levels by -56% compared to baseline.¹⁵⁸

Evinacumab has been approved by the FDA and EMA to lower LDL-C in patients aged 12 years and older with HoFH. Ongoing trials are evaluating evinacumab for paediatric patients with HoFH,¹⁵⁹ for patients with severe hypertriglyceridemia at high risk of pancreatitis,¹⁶⁰ and its long-term safety and efficacy profile.¹⁶¹

Lomitapide

Lomitapide lowers cholesterol by inhibiting the microsomal triglyceride transfer protein (MTG).^{162,163} MTP facilitates the transfer and loading of triglycerides and phospholipids onto ApoB-100 in hepatic cells' endoplasmic reticulum. Thereby the assembly of very-low-density lipoprotein (VLDL) particles, which turn into LDL-C after release into the blood serum, is inhibited. After conducting a successful dose-escalation study,¹⁶⁴ a single-arm, open-label, phase 3 study of 29 patients with HoFH showed that lomitapide

lowers LDL-C by -50% and reduces the frequency of lipid apheresis.¹⁶⁵ Due to the accumulation of lipids in hepatocytes, increased aminotransferase levels alongside gastrointestinal symptoms, which can be well managed by dose reductions or treatment suspensions, were noted in the clinical trial.

Lomitapide is approved for the treatment of HoFH adjunct to a low-fat diet and therapy with other lipid-lowering therapies by the FDA and the EMA. Lomitapide's effect on CV outcomes has not been established. Lomitapide is currently evaluated in paediatric patients with HoFH, in pregnant patients, and in a real-world evidence study.^{166–168}

Mipomersen

Mipomersen is an antisense oligonucleotide, which is administered via a weekly subcutaneous injection, inhibiting the messenger ribonucleic acid (mRNA) of ApoB-100.^{20,169} By inhibiting the synthesis of ApoB-100, mipomersen also inhibits the assembly and synthesis of VLDL, which in turn results in lower LDL-C serum concentrations. A systematic review and meta-analysis of 13 trials with a total of 1,053 patients found mipomersen significantly reduces LDL-C, total cholesterol, non-HDL-C, ApoB-100, Lp(a), triglycerides, VLDL, and ApoA-I, without effecting HDL-C.¹⁷⁰ Treatment with mipomersen was frequently associated with injection-site reactions, hepatic steatosis, elevated liver enzymes, and flu-like symptoms.¹⁷⁰

Mipomersen is approved for HoFH adjunct to lipid-lowering therapies and diet by the FDA. However, the EMA refused to grant marketing authorization due to the frequent gastrointestinal and cardiovascular side-effects observed in clinical trials, which could outweigh mipomersen's potential beneficial cardiovascular benefits. Mipomersen's long-term safety and efficacy are currently under investigation.²⁰

Volanesorsen

Volanesorsen is a second-generation hepatocyte-directed antisense oligonucleotide that reduces mRNA levels of ApoC-III. ApoC-III serves as an independent risk marker for CVD due to its central role in lipid metabolism.^{171,172} High ApoC-III levels were shown to increase total triglyceride levels by an accumulation of VLDL and chylomicrons.^{173–176} In the contrary, loss-of-function mutations of the ApoC-III are associated with a lower risk of CVD.^{177–179}

After a first proof-of-concept study,¹⁸⁰ volanesorsen's dose-dependent efficacy has been established in a phase 1 trial of three patients with familial chylomicronemia syndrome (FCS) and elevated triglycerides.¹⁸¹ In a randomized, placebo-controlled, double-blind phase 2 trial of 57 patients with elevated triglycerides, volanesorsen reduced ApoC-III by up to -80% and triglycerides by -71%.¹⁸² A similar trial design enrolling 114 patients with established CVD and elevated triglycerides, demonstrated an up to -60% reduction in triglyceride levels.¹⁸³ Consistently, volanesorsen reduced triglycerides by -71% in a trial of 114 patients with severe hypertriglyceridemia or FCS.¹⁸⁴ However, between 24% to 61% of patients treated with volanesorsen suffered from injection-site reactions. Further side effects include serious bleeding and thrombocytopenia. Volanesorsen was approved by the EMA, yet not the FDA due to safety concerns, for the treatment of patients with FCS.

Pemafibrate

Pemafibrate is a fibrate that modulates PPAR- α .¹⁸⁵ In contrast to fenofibrate, pemafibrate is selective for PPAR- α and exerts a higher potency. Based on promising results

from multiple phase 1, 2, and 3 trials,¹⁸⁵ the double-blind, randomized, placebo-controlled trial PROMINENT investigated pemafibrate's effect on MACE in 10,497 patients with diabetes mellitus type 2 and hypertriglyceridemia.^{186,187} At a median follow-up of 3.4 years, pemafibrate lowered triglycerides by -26%, VLDL by -26%, remnant cholesterol by -26%, ApoC-III by -28% compared to placebo. However, pemafibrate did not significantly reduce the risk of MACE (HR: 1.03, 95%CI: 0.91 to 1.15).

Pelacarsen

Pelacarsen is a second-generation hepatocyte-directed antisense oligonucleotide that lowers Lp(a) levels.¹⁸⁸ Lp(a) has been identified as an independent risk marker for CVD as it exerts pro-atherogenic, pro-inflammatory, and pro-thrombotic effects which may play a critical role in the pathogenesis of atherosclerosis.¹⁸⁹ Patients' serum Lp(a) levels are primarily (>90%) genetically determined by the apo(a) gene.¹⁹⁰ Consequently, genetic studies found a causal link between elevated Lp(a) levels and a higher risk for CVD diseases,^{191–196} and vice versa.¹⁹⁷ However, the risk increase was of a lower magnitude than the one observed with LDL-C.^{193,198,199} In the FOURIER trial, greater MACE reductions were seen among patients whose highly elevated Lp(a) levels were reduced by evolocumab.²⁰⁰ Two studies reported a significantly lower cardiovascular event rate in patients treated with lipid apheresis for Lp(a).^{201,202} However, substantial reductions in Lp(a) levels are necessary to provide a clinically meaningful effect on cardiovascular outcomes.^{193,203}

Pre-clinical studies confirmed the concept (proof-of-concept) that antisense oligonucleotides specifically lower Lp(a) levels.^{204,205} Subsequently, phase 1 and 2 trials enrolling a total of 103 patients with elevated Lp(a) and CVD showed that treatments with antisense oligonucleotides reduced Lp(a) levels by up to -80%.^{206,207} Consistently, in a randomized, double-blind, placebo-controlled phase 2 trial of 286 patients with elevated Lp(a) levels and established CVD, pelacarsen reduced Lp(a) in a dose-dependent manner by up to -80% from baseline.¹⁸⁹ At the same time, pelacarsen was well tolerated. Only injection-site reactions were more frequently observed in the treatment group. HORIZON, the multi-centre CVOT investigating pelacarsen's effect on MACE in 7,680 patients, is currently ongoing and expected to be completed by 29th May 2025.²⁰⁸

DPA and EPA

A combination therapy of the omega-3 fatty acids EPA, DHA, and DPA is currently in clinical development. According to the manufacturer Matinas Biopharma, their product MAT9001 contains a significant amount of EPA and DPA mixed with a small dose of DHA. After promising experimental studies and a clinical pharmacokinetic trial,^{209,210} MAT9001 (4 g/d) was compared to icosapent ethyl (4 grams per day) in a phase 2 head-to-head crossover trial enrolling 42 patients with hypertriglyceridemia.²¹¹ MAT9001 achieved significantly greater reductions in triglycerides (-33% vs. -11%, $p<0.001$), VLDL-C (-33% vs. -8%, $p<0.001$), non-HDL-C (-9% vs. -5%, $p=0.027$), total cholesterol (-9% vs. -6%, $p=0.0013$), ApoC-III (-26% vs. -5%, $p=0.006$), ApoA-I (-15% vs. -10%, $p=0.003$), and PCSK9 (-12% vs. +9%, $p<0.001$), yet not ApoB-100 (-4% vs. -1%, $p=0.058$), HDL-C (-11% vs. -11%, $p=0.337$), and LDL-C (-2% vs. -4%, $p=0.116$). However, the ENHANCE-IT trial could not reproduce MAT9001's superior efficacy to icosapent ethyl in patients undergoing a therapeutic lifestyle change diet.²¹² No difference in triglyceride, LDL-C, and other lipoprotein levels could be observed between the two interventional groups except for hsCRP (-6% vs. -9%, $p=0.034$). Albeit Matinas

Biopharma planned to investigate MAT9001's efficacy in a CVOT, active clinical development has been suspended in light of the ENHANCE-IT trial.

Olezarsen

Olezarsen is a next-generation ApoC-III hepatocyte-directed antisense oligonucleotide, which is conjugated with n-acetyl galactosamine. This novel molecular design resulted in an improved efficacy and safety profile compared to volanesorsen. In a phase 1/2a trial enrolling 40 healthy volunteers, olezarsen reduced ApoC-III by up to -92% and triglycerides by -77%, whilst only one person (2.5%) suffered from an injection-site reaction.²¹³ Olezarsen, is currently investigated in five phase 2 and 3 trials for patients with (severe) hypertriglyceridemia and FCS.^{214–218}

NNC0385-0434 A

NNC0385-0434 A is the first oral PCSK9 inhibitor that is currently under phase 2 development in a trial of 255 patients with established CVD.²¹⁹ This novel route of administration is expected to improve adherence compared to PCSK9 that are currently injected subcutaneously every two to four weeks.

Olpasiran

Olpasiran is a siRNA that reduces Lp(a) levels. In pre-clinical studies olpasiran successfully reduced Lp(a) levels in transgenic mice and cynomolgus monkeys.²²⁰ In a phase 1 trial of 64 patients, olpasiran reduced Lp(a) by -71% to -97%.²²⁰ A phase 2 dose-finding study, OCEAN(a)-DOSE, of 281 patients with established CVD is currently ongoing.²²¹ Topline results “demonstrated a significant reduction from baseline in Lp(a) of up to or greater than 90 percent at week 36 (primary endpoint) and week 48 (end of treatment period) for the majority of doses.”²²²

Other therapeutics

Beyond the presented clinical development programs there are a variety of innovative small molecules, monoclonal antibodies, vaccines, and gene therapies currently in pre-clinical development.²²³

2.2 Principles of healthcare economic evaluation

A recent report from the ESC estimates that four of their high-income member countries, e.g. Switzerland, Norway, Germany, and Luxembourg, spent more than USD6,000 per capita on CVD every year.⁵ The average EU country spends 16% of its healthcare expenditure on CVD, representing the single largest therapeutic area. Beyond this direct medical expenditure, economies suffer from indirect societal costs inflicted by CVD. The European Heart Network estimates that out of the €210 billion that EU countries spent on CVD in 2015, €54 billion (26%) was due to productivity losses and €45 billion (21%) due to informal healthcare costs for CVD patients.⁵ This already significant burden of CVD on the economy is further exacerbated by socio-demographic trends towards an aging population, a transition from infectious to chronic diseases, and rising costs for healthcare products and services. Therefore, the American Heart Association estimates that the economic burden of CVD will double from USD555 billion in 2015 to USD1.1 trillion in 2035.²²⁴ Ultimately, this growing economic pressure must be addressed by policy-makers. The focus and economic spending ought to shift from CVD treatment to prevention.

The previous section shined light on the ever-growing number of new drugs that may soon come to the market for primary and secondary cardiovascular prevention in dyslipidaemia patients. The example of high-priced PCSK9 inhibitors, which were expected to quickly transform the widespread treatment of patients with hypercholesterinaemia, illustrates that the cost of new therapies must be feasible for patients and health insurers to pay for. PCSK9 inhibitors fell short of expectations as pharmaceutical companies demanded too high prices for drugs with an impractical route of administration and limited therapeutic efficacy. The resulting prolonged negotiations with insurers in the US and in the EU caused delayed access for patients. In summary, new lipid-lowering therapies must not only demonstrate clinical efficacy and safety but also cost-effectiveness to promote their widespread adoption in clinical practice. Therefore, this section provides a brief overview of healthcare economic evaluation techniques, particularly cost-effectiveness and cost-utility analyses.

2.2.1 Measuring benefits and costs

Every healthcare system in the world is constrained by its available monetary budget. This limited budget has to be spent effectively. Out of the potentially unlimited products and services, governments need to select those that most efficiently improve the health of the enrollees. Economists are then consulted to solve this dissonance by studying “how men and society end up choosing to employ scarce resources that could have alternative use.”²²⁵ In other words, a healthcare system only wants to buy and reimburse the most effective and safest products and services. Therefore, economic evaluations of these products and services are conducted to compare two or more treatment options’ costs and consequences for the individual patient and/or society.^{226,227}

Costs measurement

To evaluate which intervention is the preferred alternative, first, both interventions’ costs must be measured.²²⁸ Therefore, unit costs for the new and old interventions are sampled, e.g. it is determined how much the new and old drugs, surgeries, medical or devices cost. Thereafter, economists calculate how much it costs to treat the average patient bearing the analysed disease before and after the intervention. Besides these direct costs, indirect medical costs, e.g. time not spent at work, may also be included to calculate costs from the societal perspective rather than the healthcare system perspective.

Benefit measurement

Secondly, the benefit of all evaluated interventions should be measured to permit a standardized comparison.²²⁸ The benefit typically refers to a health gain. It is possible to simply assess how many hospitalizations a new intervention avoids. However, the gold standard is to measure the quantity and quality of health an intervention adds per patient, e.g. quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).²²⁹ Both are a composite measure of years lived with disability (YLD) – a measure of the disease’s severity – and years of life lost to premature mortality (YLL) – a measure of the burden of disease. These health-related quality of life (HRQoL) measurements are ideally captured in RCTs based on a validated scale, such as the EQ-5D.²³⁰ HRQoL measures may vary across the globe as nations, for example, assign different values to mental or physical disorders.

2.2.2 Types of economic evaluations

There are four general healthcare economic evaluation types (Table 4):^{226,227}

- The cost-minimization analysis compares the costs for interventions with the same outcome. Based on the difference in expenditure, the preferred lower-cost option can then be chosen. In practice, only a few interventions deliver the same result at different costs.
- The cost-benefit analysis (CBA) compares the costs and outcomes of interventions with each other. Benefits are measured in monetary units. The result of this analysis is the net benefit, cost-benefit ratio, or return on investment. Healthcare systems then choose the intervention that delivers the highest net benefit, the best cost-benefit ratio, or the highest return on investment.
- The cost-effectiveness analysis (CEA) also compares the costs and outcomes for interventions with each other but measures the benefits in a single, natural unit – mostly life years (LYs). The result of this analysis is the incremental cost-effectiveness ratio (ICER), which measures the incremental LYs gained compared to the incremental costs for the intervention of interest.
- The cost-utility analysis (CUA) compares the costs and outcomes of interventions. Benefits are measured as utility values to reflect the quality and quantity of life. The result of this analysis is the ICER, which measures the incremental QALYs per incremental cost. Although technically incorrect, CUA and CEA are often conducted simultaneously and therefore collectively referred to as CEA. Over the past years, a distinct set of methodologies have been developed to conduct CEA. Two interventions' benefits and costs are compared by simulating a disease's progression among a cohort of, for example, 1,000 patients. The "stochastic process" of disease progression is typically simulated in Markov models, decision trees, or a combination of these.^{231,232} These models' base case results are then scrutinized by conducting univariate and probabilistic sensitivity analyses as well as scenario and subgroup analyses.²³³ For these simulations, each country has its own sets of underlying assumptions and guidelines, which are typically determined and published by the national health technology assessment agency.²³⁴

Evaluation Type	Cost measurement	Benefit measurement	Result
Cost-minimization analysis	Monetary unit	None	Cost difference
Cost-benefit analysis (CBA)	Monetary unit	Monetary unit	Net benefit, benefit-to-cost, ROI
Cost-effectiveness analysis (CEA)	Monetary unit	LYs, clinical measure	ICER (cost per LY)
Cost-utility analysis (CUA)	Monetary unit	QALYs	ICER (cost per QALY)

Table 4: Types of healthcare economic evaluations

ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year, LY life year, ROI return on investment.

2.2.3 Decision-making principles

The decision principles for the cost-minimization and cost-benefit analyses are fairly simple: choose the intervention with the lowest cost or highest benefit, respectively. However, decision-making under CEA and CUA is more complex.²²⁸ The structure of decisions under these methods is presented in Table 5. Interventions that cost more yet deliver an inferior benefit than the alternative should not be reimbursed. Interventions that cost less yet offer a superior benefit should always be reimbursed. For interventions that offer a superior benefit at a higher cost or an inferior benefit at a lower cost, the decision to reimburse the new intervention depends on the nation's willingness-to-pay (WTP) threshold. The WTP threshold quantifies how much the citizens of a country want to pay for each additional LY or QALY gained. These thresholds vary across countries but are typically correlated to a country's gross domestic product (GDP).²³⁵ Interventions that exceed this WTP threshold should not be reimbursed given that the public does not want to pay for this expensive new technology. Interventions that are below this WTP threshold should be reimbursed. After conducting CBA, CUA, or CEA, governments often negotiate prices with pharmaceutical companies for new drugs. With the negotiated price discounts, governments aim to set the ICER to a level acceptable within their WTP threshold. The WTP threshold is 20,000 to 30,000 £/QALY in the UK or 100,000 to 150,000 USD/QALY in the US.²³⁵ These WTP thresholds are often subject to additional social value judgements characterising the disease's unmet need and severity treated by the analysed intervention.²³⁶

Δ Cost	Δ Benefit	ICER	Reimburse new intervention?
Positive	Negative	Negative	No
Negative	Positive	Negative	Yes
Negative	Negative	Positive	Depends on WTP threshold
Positive	Positive	Positive	Depends on WTP threshold

Table 5: Decision-making rules for cost-effectiveness analyses

Incremental costs and benefits compared to the existing therapy. *ICER* incremental cost-effectiveness ratio, *WTP* willingness-to-pay.

2.3 Context of this dissertation

This dissertation's introduction shed light on current developments in the field of lipidology. Globally, the incidence and burden of CVD are rising. Particularly patients with elevated LDL-C levels despite treatment with statins remain at high residual risk for adverse cardiovascular events, such as myocardial infarction and stroke. The pharmaceutical industry responded to this unmet medical need by developing novel therapeutics with innovative mechanisms of action. However, these novel treatments cannot be purchased at "any price". In addition to demonstrating clinical safety and efficacy in RCTs, new treatments must demonstrate cost-effectiveness to promote long-term adoption by patients and physicians.²² Otherwise, highly-priced drugs that are safe and effective to use, will not be reimbursed by insurers, prescribed by physicians, and taken by patients. "A drug that cannot be purchased offers no value to patients."²³⁷

The recent developments surrounding icosapent ethyl in Germany highlight the significance of economic considerations in medical practice.²³⁸ The pharmaceutical company Amarin entered the German market with its product icosapent ethyl (Vazkepa®) in September 2021. In February 2022, the Federal Joint Committee ("Gemeinsame

Bundesausschuss”), which is responsible for the clinical assessment and price negotiations of new drugs in Germany, concluded that icosapent ethyl’s benefit could not be proven. The Committee was concerned that according to current guidelines, more patients in the REDUCE-IT trial should have received ezetimibe to lower LDL-C levels under 70 or even 55 mg/dL – implicitly suggesting that icosapent ethyl’s MoA is mainly derived from its effect on LDL-C. However, at the start of the REDUCE-IT trial guidelines have not yet recommended LDL-C levels below 55 mg/dL. This new target LDL-C level was only determined in ESC guidelines after the publication of the REDUCE-IT trial. Furthermore, leading cardiologists and several experts present at the Federal Joint Committee’s hearing for icosapent ethyl noted that EPA acts via a novel MoA, which is distinct from simply lowering LDL-C or triglyceride levels. EPA’s novel atheroprotective pleiotropic MoA should be viewed as distinct from traditional lipid-lowering drugs. Although up to 878,000 patients could benefit from icosapent ethyl, this dispute resulted in Amarin withdrawing its product from the German market in September 2022 as it would not be able to set its price at the proposed cost of 3,080€ under the German drug pricing regulation (“Arzneimittelmarktneuordnungsgesetz” – AMNOG).^{238,239} In summary, the cases of PCSK9 inhibitors and icosapent ethyl highlight the importance of evidence and cost considerations in cardiologists’ daily practice. Healthcare systems must find a balance between practicing evidence-based medicine to reimburse safe, effective, and affordable drugs, yet at the same time providing financial incentives for pharmaceutical companies that fuel the biotechnological innovation of the future.

At the core of these conflicting interests must be one underlying consideration: patients’ benefit. This dissertation, therefore, aims to reconcile this dispute between corporates’ and insurers’ financial interests by developing a methodology and conducting an analysis that guides negotiations between insurers and corporations to expedite patient access to promising new drugs. The purpose of this dissertation is to assess the cost-effectiveness of lipid-lowering drugs for primary and secondary cardiovascular prevention in two distinct countries – Germany and the UK. Germany and the UK were chosen due to their different healthcare systems and distinct pricing, reimbursement, and coverage decisions for new drugs. In Germany, “citizens must either join the contribution-based social health insurance (SHI) or the risk-related, premium-based, private health insurance (PHI)” administered by “autonomous self-governing bodies within [a] well-designed legal framework.”²⁴⁰ In contrast, the UK’s healthcare system is funded by government taxes and is centrally administered by the National Health System (NHS). The results of this dissertation support and educate insurers, health technology agencies, and policy-makers in both countries to negotiate pricing, reimbursement, and coverage agreements with pharmaceutical companies that benefit patients. Furthermore, the methodology and models developed as part of this thesis do not only permit an assessment of established lipid-lowering therapies but will also be employed to evaluate the cost-effectiveness of emerging lipid-lowering therapies as soon as their CVOT are completed.

The following two chapters present two original research articles that analyse the cost-effectiveness of lipid-lowering therapies for primary and secondary cardiovascular prevention in Germany and the UK. Both articles provide a detailed description of the developed methodology, followed by a presentation of results, and a discussion of the analyses’ main findings and limitations in context with previous literature. The attached author contribution statements confirm that my, Daniel Tobias Michaeli, contribution to both peer-reviewed publications by far exceeded 50%. In collaboration with my co-authors, we developed the concept and design of both cost-effectiveness studies. I

was solely responsible for developing the Markov model, data collection, statistical analysis, and drafting of the manuscripts. I lead both studies' analysis and interpretation of data. Both studies were supervised and critically revised for intellectual content in scientific discourse with my co-authors.

3 Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention in Germany

3.1 Abstract

Purpose: Novel pharmaceutical treatments reducing cardiovascular events in dyslipidaemia patients must demonstrate clinical efficacy and cost-effectiveness to promote long-term adoption by patients, physicians, and insurers.

Objective: To assess the cost-effectiveness of statin monotherapy compared to additive lipid-lowering therapies for primary and secondary cardiovascular prevention from the perspective of Germany's healthcare system.

Methods: Transition probabilities and hazard ratios were derived from cardiovascular outcome trials for statin combinations with icosapent ethyl (REDUCE-IT), evolocumab (FOURIER), alirocumab (ODYSSEY), ezetimibe (IMPROVE-IT), and fibrate (ACCORD). Costs and utilities were retrieved from previous literature. The incidence of major adverse cardiovascular events was simulated with a Markov cohort model. The main outcomes were the ICER per QALY gained.

Results: For primary prevention, the addition of icosapent ethyl to statin generated 0.70 QALY and €15,717 costs (ICER: 22,352), whereas fibrates yielded 0.38 QALY and -€28,508 costs (ICER: -74,978). For secondary prevention, the addition of ezetimibe to statin provided 0.24 QALY at savings of -€9,708 (ICER: -39,731) and icosapent ethyl yielded 1.00 QALY and €6,850 costs (ICER: 6,851). PCSK9 inhibitors offered 0.63 and 0.82 QALY at costs of €41,840 and €74,825 for evolocumab (ICER: 66,893) and alirocumab (ICER: 91,441), respectively. For secondary prevention, a 95% probability of cost-effectiveness was surpassed at €19,000 for icosapent ethyl (primary prevention: €30,000), €138,000 for alirocumab, and €116,000 for evolocumab.

Conclusions: For primary cardiovascular prevention, a combination therapy of icosapent ethyl plus statin is a cost-effective use of resources compared to statin monotherapy. For secondary prevention, icosapent ethyl, ezetimibe, evolocumab, and alirocumab increase patient benefits at different economic costs.

3.2 Key points

- For primary cardiovascular prevention a combination of icosapent ethyl plus statin is a cost-effective use of resources (ICER: 22,352 €/QALY) in Germany.
- For secondary cardiovascular prevention, icosapent ethyl (ICER: 14,485 €/QALY), ezetimibe (ICER: -39,731 €/QALY), evolocumab (ICER: 66,893 €/QALY), and alirocumab (ICER: 91,441 €/QALY) are cost-effective treatment options.

3.3 Introduction

CVD remain the leading cause of death in Germany, accounting for more than 35% of all fatalities.²⁴¹ Besides adverse health effects for the individual, CVD lead to rising medical costs for society.²⁴² The American Heart Association identified the ongoing demographic shift, increasing prevalence, and rising treatment costs as the main drivers for surging CVD expenses.²²⁴

For patients with elevated triglycerides and cholesterol, treatment strategies for primary and secondary cardiovascular prevention include lipid-lowering drugs. Since the launch of statins more than 25 years ago, several additive therapies were introduced. However, only ezetimibe, icosapent ethyl, evolocumab, and alirocumab significantly reduced the risk of MACE by -6% (95% CI: -1 to -11, $p=0.016$), -25% (95% CI: -17 to -32, $p<0.001$), -15% (95% CI: -8 to -21, $p<0.001$), and -15% (95% CI: -7 to -22, $p<0.001$), respectively.^{67,113,243,244}

In line with each drug's label, the ESC recommends individualized dyslipidaemia treatment strategies depending on patient-specific plasma cholesterol and triglyceride levels. This distinction matters as elevated LDL-C levels adversely impact 10-year patient survival. For our analyses, we therefore categorized treatment options in cholesterol-lowering (ezetimibe, alirocumab, and evolocumab) and triglyceride-lowering (icosapent ethyl and fibrates) strategies based on ESC guidelines.²⁰

3.3.1 Cholesterol-lowering strategy

A combination of statin plus ezetimibe is indicated for very high-risk patients who do not achieve their cholesterol treatment goals under the maximum tolerable statin monotherapy. If the predefined LDL-C levels are still not attained under an ezetimibe plus statin combination, doctors may further prescribe PCSK9 inhibitors.

3.3.2 Triglyceride-lowering strategy

In contrast, icosapent ethyl plus statin is recommended in high-risk patients with elevated triglyceride levels despite statin monotherapy treatment. Similarly, fibrates may be used to supplement statin monotherapy in high-risk patients with elevated triglyceride levels.

The recent launch of icosapent ethyl in Europe combined with pricing disputes surrounding PCSK9 antibodies and genericization of ezetimibe warrant a cost-effective-

ness analysis of existing lipid-lowering therapies. This study examines the cost-effectiveness of additive lipid-lowering therapies compared to statin monotherapy for primary and secondary cardiovascular prevention from the perspective of the German healthcare system. Whilst previous studies mostly focused on one particular drug for secondary prevention, this is the first study assessing the clinical economics of five lipid-lowering therapeutics in both primary and secondary prevention.

3.4 Data and methods

3.4.1 Model structure

A Markov model comparing statin monotherapy with statin combination therapies (icosapent ethyl, PCSK9 inhibitors, ezetimibe, and fibrates) for cardiovascular prevention was constructed with Microsoft Excel (2016). The model entails three underlying health states: “Alive without CVD”, “Alive with CVD”, and “Dead” (Figure 3). Patients without CVD were at risk to experience a non-fatal myocardial infarct (MI) or non-fatal stroke, which directed them to the “Alive with CVD” state. All alive patients were also at risk to die from CVD or non-CVD causes, which channelled them to the death state. All alive patients were at risk for hospitalization for unstable angina and coronary revascularization, yet these events did not alter their underlying health state. Primary prevention patients started the model in the “Alive without CVD” state, whereas secondary prevention patients began the model in the “Alive with CVD state”. In line with the Institute for Quality and Efficiency in Health Care (IQWiG) guidelines, the model was constructed from the perspective of the German healthcare system with a discount rate of 3% for utilities and costs.²⁴⁵

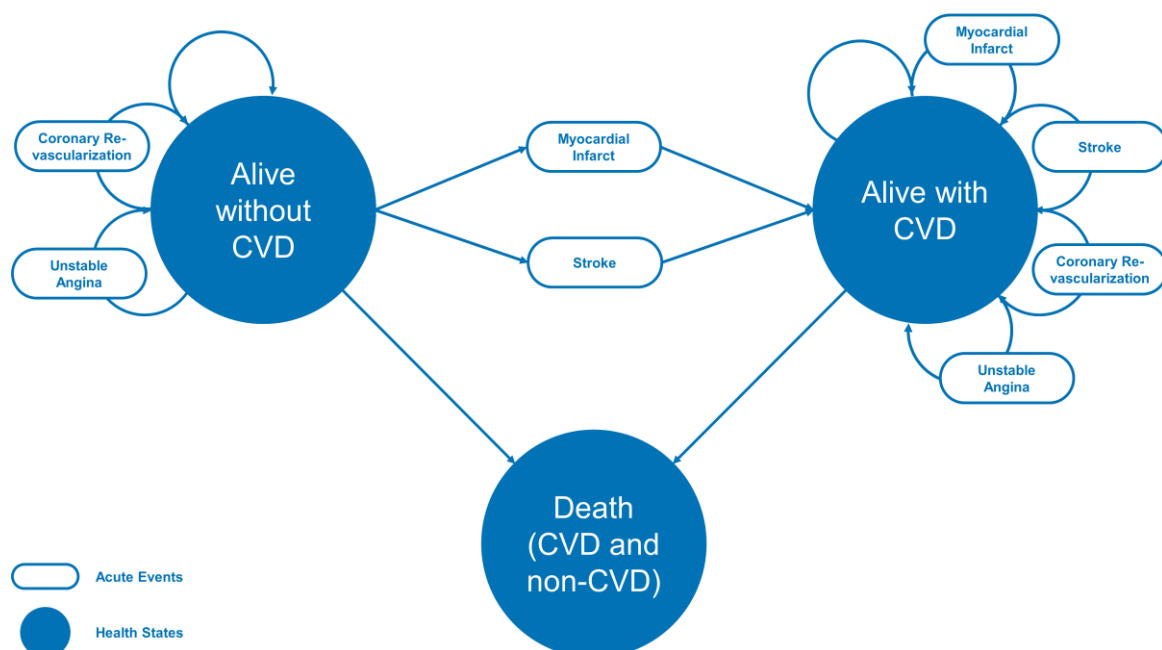


Figure 3: Markov model structure of health states and acute cardiovascular events

The Markov model illustrates health states of the stimulated cohort defined as “Alive without CVD”, “Alive with CVD”, and “Death”. In any cycle, individuals were at risk for acute cardiovascular events: myocardial infarction, stroke, coronary revascularization, and unstable angina. CVD cardiovascular disease.

3.4.2 Evaluated treatment options

All lipid-lowering drugs that were approved by the EMA for primary or secondary cardiovascular prevention in combination treatment with statins after the year 2000 were included. For every metabolic agent, the largest (in terms of enrolled patients) available randomized clinical trial reporting MACE was considered (Table 6). Icosapent ethyl and fibrate were the only treatments with available data for primary cardiovascular prevention. Ezetimibe, icosapent ethyl, evolocumab, alirocumab, and fibrate were evaluated for secondary cardiovascular prevention. No endpoint studies were completed for bile acid sequestrants, inclisiran, and bempedoic acid to date. A fixed combination of nicotinic acid and laropiprant was excluded due to the negative recommendation issued by the EMA in 2012 following the HPS2-THRIVE study.¹³²

3.4.3 Transition probabilities

Transition probabilities were derived from CVOT for icosapent ethyl (REDUCE-IT), evolocumab (FOURIER), alirocumab (ODYSSEY), ezetimibe (IMPROVE-IT), and fibrate (ACCORD).^{67,102,113,243,244} All trials reported separate outcomes for non-fatal MI, non-fatal stroke, hospitalization for unstable angina, coronary revascularization, CVD death, and non-CVD death. Extracted outcomes were transformed to 1-year transition probabilities based on the median follow-up time from CVOT (Table 7).

Parameter	Icosapent Ethyl			Evolocumab			Alirocumab			Ezetimibe			Fibrate			Distribution
	Value	Variation	Ref.	Value	Variation	Ref.	Value	Variation	Ref.	Value	Variation	Ref.	Value	Variation	Ref.	
HAZARD RATIOS																
Alive without CVD (primary prevention)																
Non-fatal MI	0.78	(0.67,0.90)	113	NA	NA	243	NA	NA	244	NA	NA	67	0.98	(0.84,1.13)	102	Normal
CVD death	0.90	(0.77,1.04)	113	NA	NA	243	NA	NA	244	NA	NA	67	0.92	(0.78,1.06)	102	Normal
Non-CVD death	1.14	(0.97,1.31)	113	NA	NA	243	NA	NA	244	NA	NA	67	1.03	(0.87,1.18)	102	Normal
Non-fatal stroke	0.81	(0.69,0.93)	113	NA	NA	243	NA	NA	244	NA	NA	67	1.13	(0.96,1.29)	102	Normal
Hospitalization for unstable angina	0.76	(0.64,0.87)	113	NA	NA	243	NA	NA	244	NA	NA	67	1.05	(0.89,1.21)	102	Normal
Coronary revascularization	0.76	(0.64,0.87)	113	NA	NA	243	NA	NA	244	NA	NA	67	1.06	(0.90,1.21)	102	Normal
Alive with CVD (secondary prevention)																
Non-fatal MI	0.68	(0.58,0.79)	113	0.72	(0.64,0.81)	243	0.86	(0.77,0.96)	244	0.87	(0.80,0.95)	67	0.88	(0.75,1.01)	102	Normal
CVD death	0.79	(0.67,0.91)	113	1.05	(0.88,1.25)	243	0.88	(0.74,1.05)	244	1.00	(0.89,1.13)	67	0.82	(0.70,0.95)	102	Normal
Non-CVD death	1.01	(0.85,1.16)	113	1.04	(0.91,1.19)	243	0.78	(0.66,0.94)	244	0.98	(0.90,1.06)	67	0.92	(0.79,1.06)	102	Normal
Non-fatal stroke	0.71	(0.60,0.82)	113	0.91	(0.78,1.07)	243	0.73	(0.57,0.93)	244	0.86	(0.73,1.00)	67	1.01	(0.86,1.17)	102	Normal
Hospitalization for unstable angina	0.67	(0.57,0.77)	113	0.99	(0.82,1.18)	243	0.61	(0.41,0.92)	244	1.06	(0.85,1.33)	67	0.94	(0.80,1.08)	102	Normal
Coronary revascularization	0.66	(0.56,0.75)	113	0.78	(0.71,0.86)	243	0.88	(0.79,0.97)	244	0.96	(0.90,1.02)	67	0.94	(0.80,1.08)	102	Normal
UTILITIES																
Alive without CVD																
65-70 years	0.65	(0.64,0.67)	246	0.65	(0.64,0.67)	246	0.65	(0.64,0.67)	246	0.65	(0.64,0.67)	246	0.65	(0.64,0.67)	246	Beta
70+ years	0.63	(0.62,0.65)	246	0.63	(0.62,0.65)	246	0.63	(0.62,0.65)	246	0.63	(0.62,0.65)	246	0.63	(0.62,0.65)	246	Beta
Alive with CVD																
65-70 years	0.57	(0.56,0.59)	247	0.57	(0.56,0.59)	247	0.57	(0.56,0.59)	247	0.57	(0.56,0.59)	247	0.57	(0.56,0.59)	247	Beta
70+ years	0.55	(0.54,0.57)	247	0.55	(0.54,0.57)	247	0.55	(0.54,0.57)	247	0.55	(0.54,0.57)	247	0.55	(0.54,0.57)	247	Beta
Decrements																
Non-fatal MI	0.04	(0.02,0.05)	248	0.04	(0.02,0.05)	248	0.04	(0.02,0.05)	248	0.04	(0.02,0.05)	248	0.04	(0.02,0.05)	248	Gamma
Non-fatal stroke	0.12	(0.09,0.16)	248	0.12	(0.09,0.16)	248	0.12	(0.09,0.16)	248	0.12	(0.09,0.16)	248	0.12	(0.09,0.16)	248	Gamma
Hospitalization for unstable angina	0.09	(0.06,0.13)	248	0.09	(0.06,0.13)	248	0.09	(0.06,0.13)	248	0.09	(0.06,0.13)	248	0.09	(0.06,0.13)	248	Gamma
Coronary revascularization	0.01	(0.01,0.03)	248	0.01	(0.01,0.03)	248	0.01	(0.01,0.03)	248	0.01	(0.01,0.03)	248	0.01	(0.01,0.03)	248	Gamma
COSTS																
Alive without CVD	4,522	(±25%)	249	4,522	(±25%)	249	4,522	(±25%)	249	4,522	(±25%)	249	4,522	(±25%)	249	Gamma
Alive with CVD	8,008	(±25%)	250,251	8,008	(±25%)	250,251	8,008	(±25%)	250,251	8,008	(±25%)	250,251	8,008	(±25%)	250,251	Gamma
Non-fatal MI	8,588	(±25%)	251	8,588	(±25%)	251	8,588	(±25%)	251	8,588	(±25%)	251	8,588	(±25%)	251	Gamma
CVD death	11,842	(±25%)	250-253	11,842	(±25%)	250-253	11,842	(±25%)	250-253	11,842	(±25%)	250-253	11,842	(±25%)	250-253	Gamma
Non-CVD death	3,924	(±25%)	252-254	3,924	(±25%)	252-254	3,924	(±25%)	252-254	3,924	(±25%)	252-254	3,924	(±25%)	252-254	Gamma
Non-fatal stroke	10,441	(±25%)	251	10,441	(±25%)	251	10,441	(±25%)	251	10,441	(±25%)	251	10,441	(±25%)	251	Gamma
Hospitalization for unstable angina	4,791	(±25%)	250	4,791	(±25%)	250	4,791	(±25%)	250	4,791	(±25%)	250	4,791	(±25%)	250	Gamma
Coronary revascularization	9,901	(±25%)	250	9,901	(±25%)	250	9,901	(±25%)	250	9,901	(±25%)	250	9,901	(±25%)	250	Gamma
Annual treatment cost	3,770		255	5,880		256	7,509		256	156		256	130		255	Fixed
Annual statin cost	132		256	132		256	132		256	132		256	132		256	Fixed
OTHERS																
Discount Rate	0.03	(0.00,0.10)	245	0.03	(0.00,0.10)	245	0.03	(0.00,0.10)	245	0.03	(0.00,0.10)	245	0.03	(0.00,0.10)	245	Fixed
Annual risk increase	0.10		257	0.10		257	0.10		257	0.10		257	0.10		257	Fixed

Table 6: Model input parameters: base case value, variation, and distribution for hazard ratios, utilities, and costs

The table displays each drug's key input parameters used for the base case scenario of the cost-effectiveness model. Variation columns display the upper and lower bound of parameter values that were used for sensitivity analyses. For hazard ratios and utilities, this variation equates to the 95% confidence interval extracted from cited references. All costs are presented in Euros (€) and are inflation-adjusted to 2021 values. Transition probabilities for the model are presented in Table 7. No clinical trial data were available for ezetimibe, alirocumab, and evolocumab in the primary prevention setting. CVD cardiovascular disease, MI myocardial infarction, NA not applicable.

Evolocumab, alirocumab, and ezetimibe therapies only investigated cardiovascular protection in patient populations with diagnosed CVD. Consequently, transition probabilities were only applied to the secondary prevention model. The REDUCE-IT and ACCORD trial analysed cardiovascular risk protection of icosapent ethyl and fibrates in both primary and secondary prevention. Therefore, separate transition probabilities for primary and secondary prevention were calculated based on a methodology described by Ademi et al. (2020).¹²⁴ The methodology derived distinct probabilities based on the baseline prevalence of CVD, primary composite outcomes for CVD and non-CVD patients, and relative risk of events for CVD and non-CVD patients. For icosapent ethyl, we accounted for the inappropriate use of the placebo comparator “mineral oil” by reducing transition probabilities in the control arm by 7% as proposed by Doi et al. (2021).^{113,120,258}

	Icosapent Ethyl		Evolocumab		Alirocumab		Ezetimibe		Fibrate	
	Treat- ment + Statin	Statin	Treat- ment + Statin	Statin	Treat- ment + Statin	Statin	Treat- ment + Statin	Statin	Treat- ment + Statin	Statin
Primary Prevention										
Non-fatal MI	0.0121	0.0154	NA	NA	NA	NA	NA	NA	0.0094	0.0096
CVD death	0.0064	0.0071	NA	NA	NA	NA	NA	NA	0.0053	0.0058
Non-CVD death	0.0037	0.0032	NA	NA	NA	NA	NA	NA	0.0056	0.0055
Non-fatal stroke	0.0036	0.0045	NA	NA	NA	NA	NA	NA	0.0027	0.0024
Hospitalization for unstable angina	0.0040	0.0052	NA	NA	NA	NA	NA	NA	0.0081	0.0078
Coronary revascularization	0.0142	0.0187	NA	NA	NA	NA	NA	NA	0.0297	0.0282
Secondary Prevention										
Non-fatal MI	0.0187	0.0274	0.0148	0.0205	0.0244	0.0283	0.0183	0.0212	0.0215	0.0244
CVD death	0.0099	0.0125	0.0084	0.0080	0.0092	0.0104	0.0102	0.0102	0.0120	0.0146
Non-CVD death	0.0056	0.0056	0.0064	0.0062	0.0036	0.0046	0.0130	0.0132	0.0127	0.0137
Non-fatal stroke	0.0055	0.0078	0.0058	0.0064	0.0042	0.0058	0.0055	0.0065	0.0061	0.0060
Hospitalization for unstable angina	0.0061	0.0091	0.0078	0.0080	0.0014	0.0023	0.0029	0.0027	0.0185	0.0196
Coronary revascularization	0.0220	0.0336	0.0257	0.0330	0.0287	0.0327	0.0385	0.0406	0.0727	0.0775

Table 7: Transition probabilities between health states and for acute cardiovascular events

Transition probabilities were derived from cardiovascular outcome trials for each treatment option: Icosapent ethyl (REDUCE-IT), evolocumab (FOURIER), alirocumab (ODYSSEY), ezetimibe (IMPROVE-IT), and fibrates (ACCORD).^{67,102,113,243,244} MI myocardial infarction, CVD cardiovascular disease.

One-year transition probabilities were employed for the first cycle period. Thereafter, probabilities adjust for the increasing MACE and mortality risks derived from German mortality data. Risks were increased by 10% per year.

Steen et al. showed that the risk of experiencing a recurrent cardiovascular event after an acute coronary syndrome (ACS) is substantially higher in the period directly after the ACS.²⁵⁹ In their study of 239,234 US patients, Steen et al. observed an approximately 6-fold greater risk of MACE immediately after patients were hospitalized with an ACS. Consequently, in the present model, MACE transition probabilities were adjusted for this 6-fold risk increase in the period following an ACS.

3.4.4 Model population

The model population features distinct patient populations and transition probabilities for each evaluated treatment alternative. Coherent with the weighted-average patient age of all examined trials, the simulated cohort entered the model at the age of 63 years. The model simulated 27 one-year cycles until the age of 90 years.

3.4.5 Utilities

Age-specific HRQoL values for the “Alive without CVD” state were extracted from a longitudinal survey of 7,708 individuals in Germany.²⁶⁰ The utility value of the “Alive with CVD” state was subsequently reduced by -0.08.²⁴⁷ We assigned a utility value of 0 to the “Death” state.

Upon the occurrence of adverse cardiovascular events, the HRQoL was reduced for the respective cycle. Utility decrements were applied for non-fatal MI (-0.04), non-fatal stroke (-0.12), hospitalization for angina (-0.09), and coronary revascularization (-0.01).¹²⁴

3.4.6 Costs

The economic burden of CVD and adverse events in Germany was extracted from previous literature. Annual costs for the “Alive without CVD” state of €4,522 are based on the cost of treating dyslipidemia and related comorbidities, e.g. diabetes and hypertension.²⁴⁹ Treatment costs for non-fatal cardiovascular events were extracted from peer-reviewed publications.^{250,251} The annual treatment costs of the “Alive with CVD” state were estimated at €8,088. This estimate is based on the average treatment cost of CVD one year post-occurrence.²⁵⁰ Consequently, the cost of MI, strokes, heart failure, and peripheral artery disease were weighted by their respective prevalence among the secondary prevention cohort in the REDUCE-IT, IMPROVE-IT, FOURIER, and ODYSSEY trials.

We estimated costs associated with dying based on the location and cause of death. Expenses were weighted by the location of death as a German large-scale study (n = 59,922) found that 71% of patients die in hospitals/institutions and 29% at home.²⁵³ Non-CVD hospital deaths were approximated with the average expense of hospital stays in Germany (€4,968),²⁵⁴ while CVD hospital deaths are based on the weighted expense of fatal MI, strokes, and ischaemic heart disease (€16,120).²⁵¹ Expenses for the last week of life at home amount to €1,369 in Germany.²⁵² All costs were adjusted for inflation to 2021 values.

Annual treatment costs for statins (€131.62), ezetimibe (€156.48), evolocumab (€5,879.54), alirocumab (€7,508.88), and fibrates (€130.44) were extracted from a German statutory insurance price schedule.²⁵⁶ Annual treatment costs for icosapent ethyl (€2,400) were set based on manufacturer guidance.²⁶¹

3.4.7 Outcomes

The principal outcomes were the ICER derived from QALYs and LYs gained. Numbers needed to treat (NNT) were furthermore compared across events and treatment strategies.

3.4.8 Scenario, sensitivity, willingness-to-pay, and pricing analyses

First, uncertainty surrounding input parameters was assessed in a univariate (one-way) sensitivity analysis. In addition, the impact of variations in drug price, discount

rate, time horizon, and mortality trends was examined in a scenario analysis. A probabilistic sensitivity analysis (PSA) featuring 1,000 runs evaluates the uncertainty of input parameters concurrently. A WTP analysis was conducted to estimate the ICER at which the probability of treatments being cost-effective surpasses 95%. Lastly, we evaluated the impact of drug pricing on calculated cost-effectiveness ratios.

3.5 Results

3.5.1 Base case analysis

Base case results are presented on the cost-effectiveness plane in Figure 4 and Figure 5. In the primary prevention setting, the addition of icosapent ethyl to statin generated 0.70 additional QALY and €15,717 costs (ICER: 22,352 €/QALY). The addition of fibrate to statin yielded 0.38 incremental QALY and -€28,508 costs (ICER: -74,978 €/QALY) (Table 8).

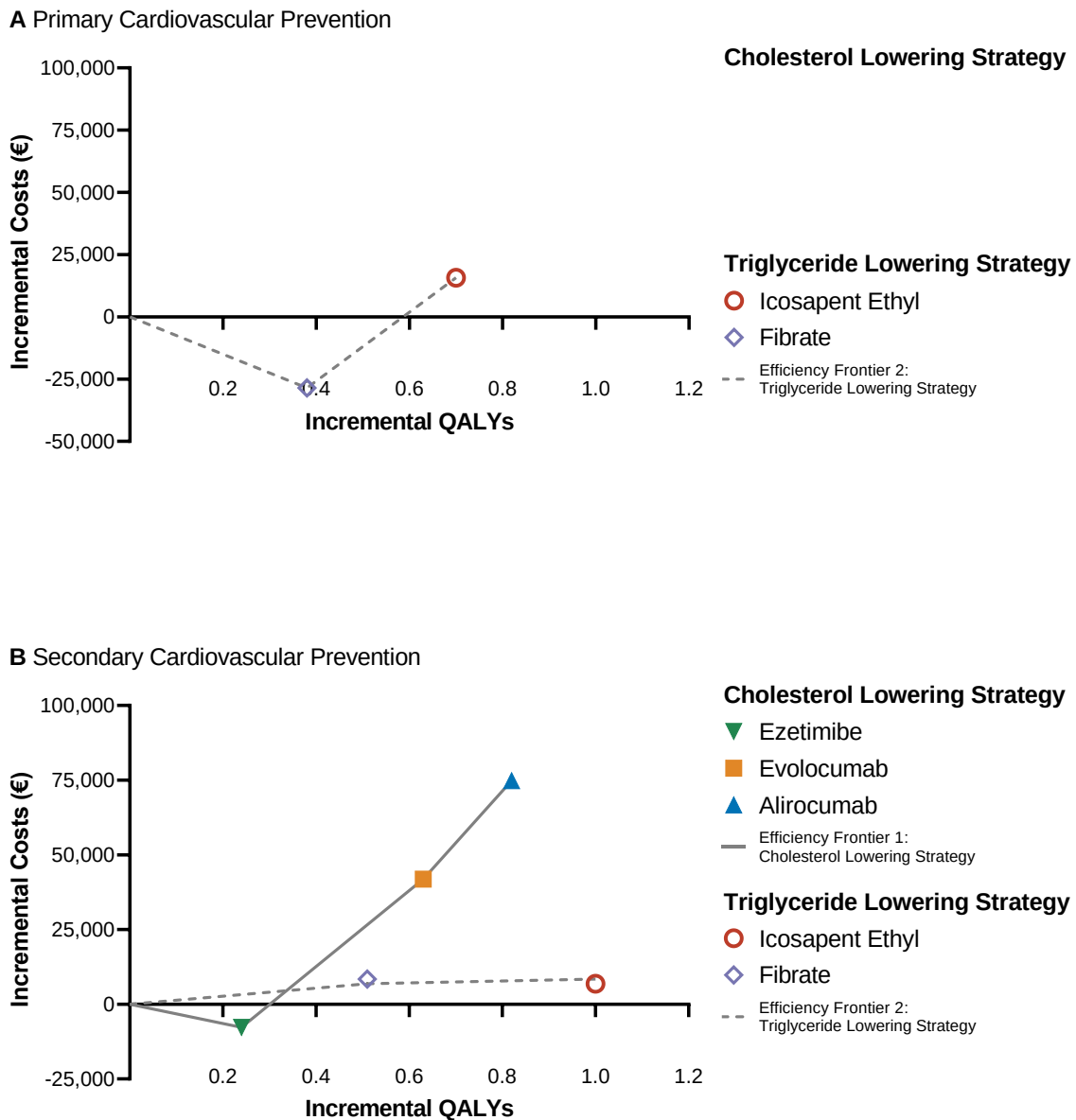


Figure 4: Cost-effectiveness plane with efficiency frontier for cholesterol- and triglyceride-lowering treatment strategies in combination with statin

Results are visualized for primary (A) and secondary cardiovascular prevention (B). All costs are presented in Euros (€) and inflation-adjusted to 2021 values. QALYs and costs are displayed per person. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines.²⁰ QALY quality-adjusted life year.

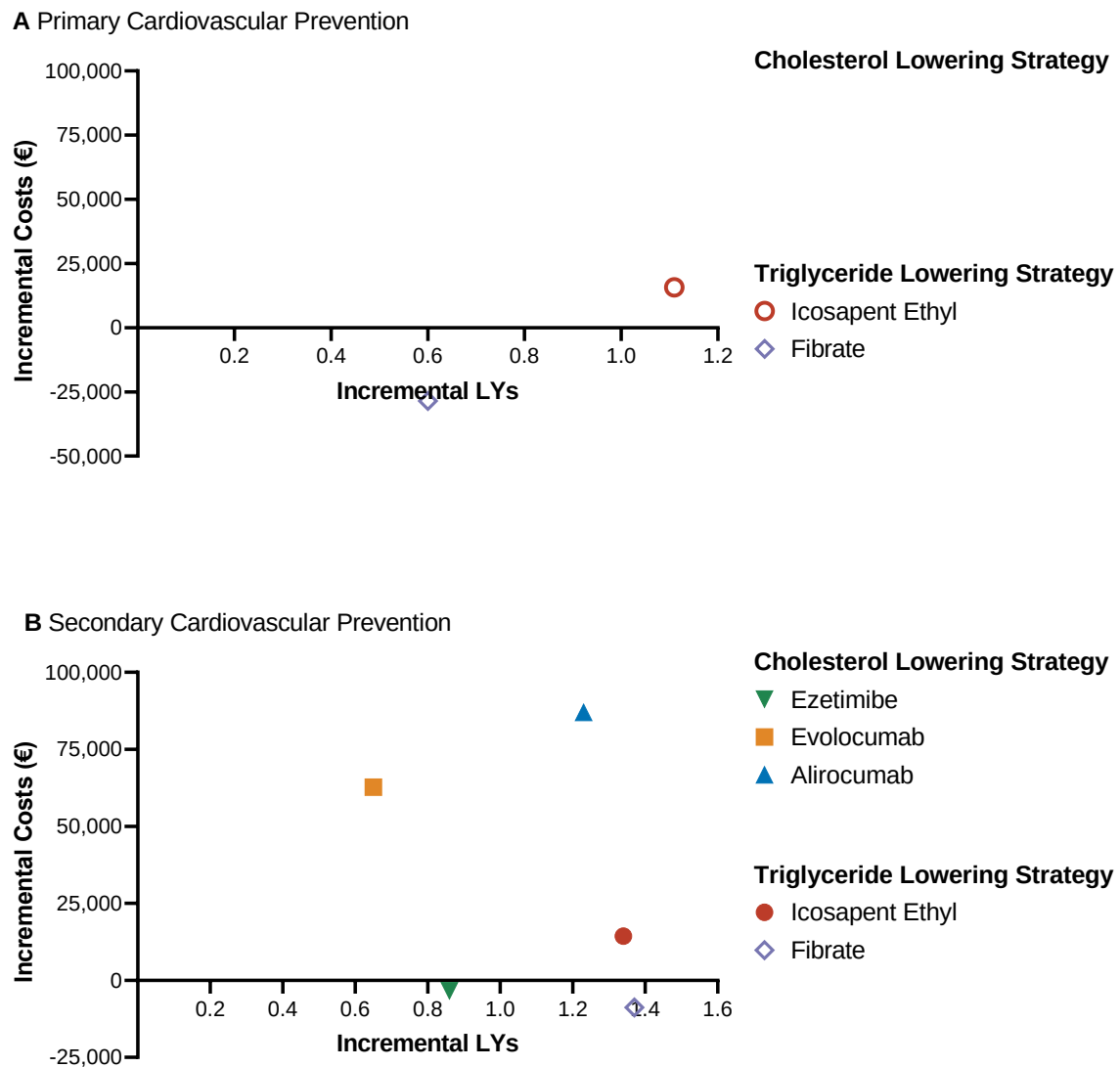


Figure 5: Cost-effectiveness plane with efficiency frontier for cholesterol- and triglyceride-lowering treatment strategies in combination with statin by life years gained

Results are visualized for primary (A) and secondary cardiovascular prevention (B). All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. LYs and costs are displayed per person. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines.²⁰ LY life year.

In the secondary prevention setting, the addition of ezetimibe to statin generated 0.24 incremental QALY at savings of -€9,708 (ICER: -39,731 €/QALY). PCSK9 inhibitors offered QALY gains of 0.63 and 0.82 at costs of €41,840 and €74,825 for evolocumab (ICER: 66,893 €/QALY) and alirocumab (ICER: 91,441 €/QALY), respectively. Icosapent ethyl provided a QALY gain of 1.00 at an expense of €6,850 (ICER: 6,851 €/QALY).

	Cholesterol-Lowering Strategy			Triglyceride-Lowering Strategy	
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fibrate
Primary Prevention					
Incremental QALYs	NA	NA	NA	0.70	0.38
Incremental LYs	NA	NA	NA	1.11	0.60
Incremental costs	NA	NA	NA	15,717	-28,508
ICER (costs / LY)	NA	NA	NA	14,131	-47,374
ICER (costs / QALY)	NA	NA	NA	22,352	-74,978
Number needed to treat (NNT)					
Non-fatal MI	NA	NA	NA	6.3	8.8
Non-fatal stroke	NA	NA	NA	-428	-134.3
Hospitalization for unstable angina	NA	NA	NA	35.8	25.4
Coronary revascularization	NA	NA	NA	8.5	6.0
Death	NA	NA	NA	-19.1	3.9
Secondary Prevention					
Incremental QALYs	0.24	0.63	0.82	1.00	0.51
Incremental LYs	0.40	1.01	1.40	1.68	0.94
Incremental costs	-9,708	41,840	74,825	6,850	8,401
ICER (costs / LY)	-24,544	41,355	53,513	4,072	8,894
ICER (costs / QALY)	-39,731	66,893	91,441	6,851	16,355
Number needed to treat (NNT)					
Non-fatal MI	4.0	1.5	48.6	2.6	-6.3
Non-fatal stroke	12.5	9.3	14.8	17.1	-11.6
Hospitalization for unstable angina	-41153	12.4	21.1	10.3	-5.1
Coronary revascularization	3.7	1.1	-55.4	2.7	-1.3
Death	19.6	12.4	51.3	43.5	-15.2

Table 8: Model base case results over a 20-year time horizon for primary and secondary cardiovascular prevention

All costs are presented in Euros (€) and inflation-adjusted to 2021 values. QALYs, LYs, and ICERs are displayed per person. No clinical trial data were available for ezetimibe, alirocumab, and evolocumab in the primary prevention setting. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines.²⁰ QALY quality-adjusted life year, LY life year, ICER incremental cost-effectiveness ratio, NNT number needed to treat, CVD cardiovascular disease, MI myocardial infarction, NA not applicable.

3.5.2 Sensitivity analyses

Results of the univariate sensitivity analysis are presented in Table 9 and Table 10. This analysis assesses the impact of one-way variations in a single input parameter on the drugs' ICER. ICERs were mainly impacted by variations in transition probabilities to acute cardiovascular events.

	Icosapent Ethyl		Fibrate	
	Lower CI	Upper CI	Lower CI	Upper CI
Cost alive with CVD	20,931	23,772	-76,436	-73,520
Cost alive without CVD	21,358	23,346	-75,952	-74,004
Cost coronary revascularization	21,765	22,939	-75,969	-73,987
Cost CVD death	14,717	29,987	-96,159	-53,797
Cost hospitalization for unstable angina	22,278	22,426	-75,094	-74,862
Cost non-CVD death	21,620	23,084	-75,607	-74,349
Cost non-fatal MI	21,801	22,903	-75,492	-74,464
Cost non-fatal stroke	22,273	22,430	-74,993	-74,963
TP alive with CVD to coronary revascularization	13,909	22,352	-74,978	142,968
TP alive with CVD to CVD death	19,867	24,751	-82,153	-67,427
TP alive with CVD to hospitalization for unstable angina	19,795	25,253	-90,271	-52,644
TP alive with CVD to non-CVD death	21,674	23,020	-78,037	-71,915
TP alive with CVD to non-fatal MI	15,076	22,352	-74,978	69,263
TP alive with CVD to non-fatal stroke	21,882	22,826	-75,072	-74,882
TP alive without CVD to coronary revascularization	21,586	23,119	-76,850	-73,094
TP alive without CVD to hospitalization for unstable angina	22,207	22,497	-75,108	-74,849
TP alive without CVD to non-CVD death	21,672	23,157	-89,287	-64,329
TP alive without CVD to non-fatal MI	15,730	30,055	-86,770	-58,817
TP alive without CVD to non-fatal stroke	20,210	24,598	-78,677	-70,913
TP alive without CVD to CVD death	18,166	28,006	-82,988	-68,963
Utility alive with CVD (+75 years)	22,352	22,352	-74,978	-74,978
Utility alive with CVD (65-75 years)	22,134	22,558	-75,687	-74,229
Utility alive without CVD (+75 years)	22,352	22,352	-74,978	-74,978
Utility alive without CVD (65-75 years)	22,080	22,610	-75,827	-74,084
Utility coronary revascularization	22,272	22,392	-75,205	-74,530
Utility hospitalization for unstable angina	22,297	22,397	-75,218	-74,690
Utility non-fatal MI	22,270	22,415	-75,176	-74,722
Utility non-fatal stroke	22,323	22,370	-74,996	-74,966

Table 9: Univariate sensitivity analysis for primary cardiovascular prevention

Results are visualized for icosapent ethyl (A) and fibrate (B). Input parameters were varied by 95% confidence intervals displayed in Table 6. All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. CVD cardiovascular disease, MI myocardial infarction, TP transition probability.

	Ezetimibe		Evolocumab		Alirocumab		Icosapent Ethyl		Fibrate	
	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI
Cost alive with CVD	-34,987	-28,441	63,622	70,163	87,986	94,896	3,449	10,252	12,637	20,073
Cost coronary revascularization	-33,936	-29,493	64,174	69,612	91,187	91,695	5,953	7,749	14,031	18,679
Cost CVD death	-42,409	-21,020	58,243	75,543	86,076	96,807	-349	14,050	12,497	20,213
Cost hospitalization for unstable angina	-31,722	-31,706	66,748	67,037	91,384	91,498	6,736	6,965	16,064	16,646
Cost non-CVD death	-32,231	-31,197	66,374	67,411	91,351	91,531	6,278	7,423	15,935	16,775
Cost non-fatal MI	-33,411	-30,017	65,203	68,582	91,185	91,697	6,090	7,611	15,990	16,720
Cost non-fatal stroke	-32,374	-31,055	66,518	67,267	91,239	91,643	6,680	7,021	16,057	16,653
TP alive with CVD to coronary revascularization	-65,817	-27,567	58,717	101,316	82,159	127,257	6,824	14,325	9,137	16,355
TP alive with CVD to CVD death	-37,875	10,319	65,262	94,699	88,494	120,525	6,851	10,454	-4,828	50,792
TP alive with CVD to hospitalization for unstable angina	-34,641	-28,412	66,893	77,134	90,102	92,816	6,851	11,909	-3,388	44,686
TP alive with CVD to non-CVD death	-71,642	-13,801	63,606	70,970	89,119	93,967	5,156	8,357	14,016	18,284
TP alive with CVD to non-fatal MI	-31,714	2,572	66,893	84,323	85,776	120,964	6,851	12,877	-7,062	50,839
TP alive with CVD to non-fatal stroke	-32,726	-30,666	65,509	68,301	90,532	92,359	6,401	7,305	15,344	17,385
Utility alive with CVD (+75 years)	-31,714	-31,714	66,893	66,893	91,441	91,441	6,851	6,851	16,355	16,355
Utility alive with CVD (65-75 years)	-32,396	-31,011	65,411	68,329	89,305	93,519	6,693	7,004	15,945	16,756
Utility coronary revascularization	-31,931	-31,293	65,808	67,452	91,301	91,512	6,813	6,869	16,240	16,589
Utility hospitalization for unstable angina	-31,721	-31,706	66,573	67,160	91,268	91,585	6,825	6,872	16,225	16,514
Utility non-fatal MI	-31,992	-31,360	66,148	67,477	91,285	91,561	6,816	6,877	16,324	16,395
Utility non-fatal stroke	-31,934	-31,380	66,491	67,156	91,145	91,634	6,832	6,863	16,304	16,434

Table 10: Univariate sensitivity analysis for secondary cardiovascular prevention

Results are displayed for icosapent ethyl (A), evolocumab (B), alirocumab (C), ezetimibe (D), and fibrate (E). Input parameters were varied by 95% confidence intervals displayed in Table 6. All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. CVD cardiovascular disease, MI myocardial infarction, TP transition probability.

The PSA with 1,000 iterations is displayed in Figure 6. The simulation yielded mean ICERs of 19,687 €/QALY (95% CI: 8,708 to 29,814) for icosapent ethyl and -15,336 €/QALY (95% CI: -96,630 to 98,711) for fibrate in the primary prevention setting. Incremental QALY gains were 0.81 (95% CI: 0.70 to 0.94) for icosapent ethyl and 0.63 (95% CI: 0.52 to 0.74) for fibrate ($p < 0.001$). In the secondary prevention setting, mean ICERs were 10,125 €/QALY (95% CI: 2,139 to 18,100) for icosapent ethyl, 78,482 €/QALY (95% CI: 55,609 to 115,654) for evolocumab, and 100,802 €/QALY (95% CI: 76,188 to 138,001) for alirocumab. Additional QALY gained were 1.01 (95% CI: 0.82 to 1.20)

for icosapent ethyl, 0.83 (95% CI: 0.61 to 1.04) for alirocumab, 0.51 (95% CI: 0.31 to 0.72) for fibrates, 0.25 (95% CI: 0.05 to 0.44) for ezetimibe, and 0.62 (95% CI: 0.41 to 0.82) for evolocumab.

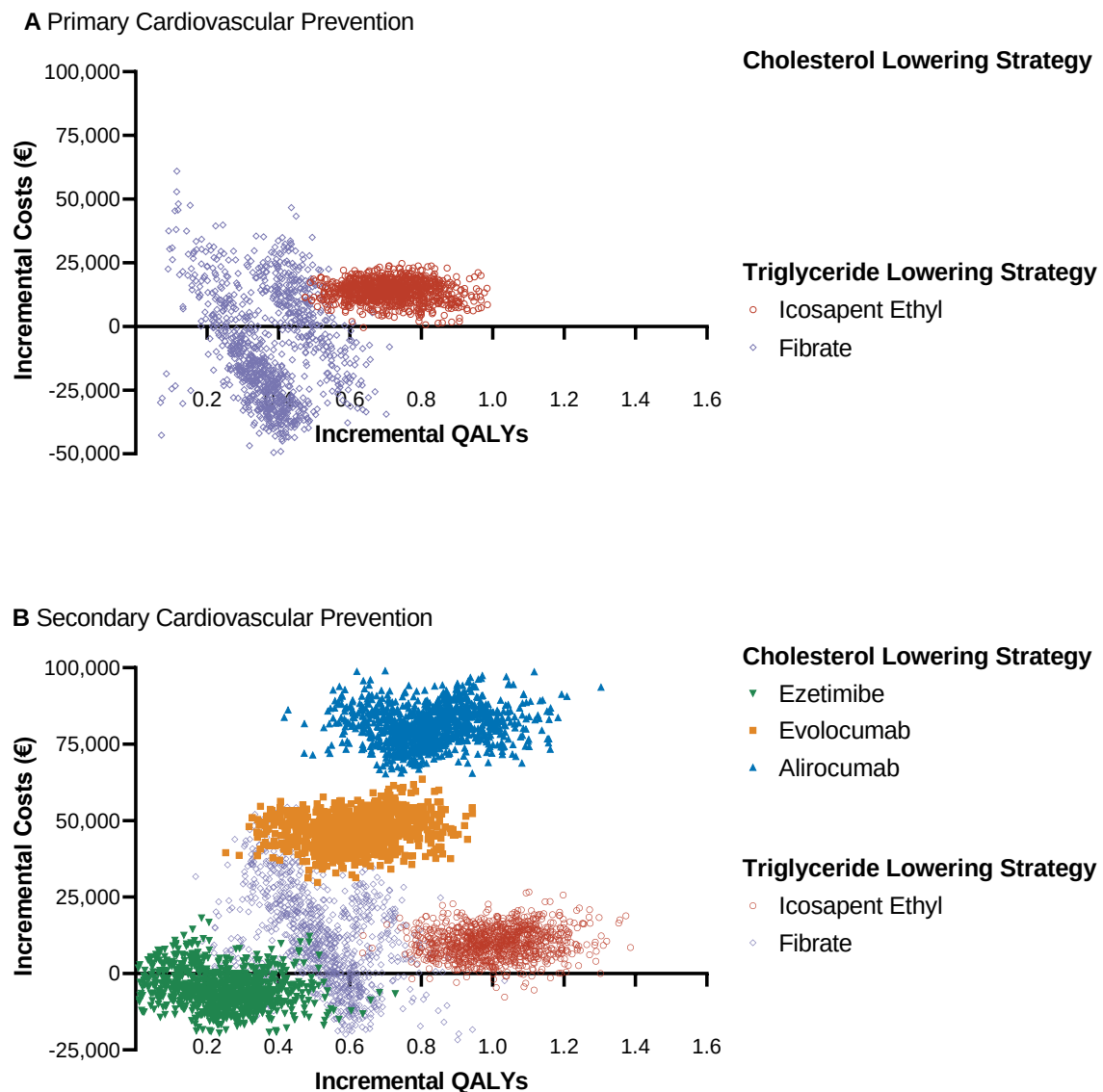


Figure 6: Probabilistic sensitivity analysis for cholesterol- and triglyceride-lowering treatment strategies in combination with statin displayed on a cost-effectiveness plane

Results are visualized for primary (A) and secondary cardiovascular prevention (B). All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. The figure displays 1,000 iterations of the conducted probabilistic sensitivity analysis which simultaneously varies input parameters by their confidence intervals and defined distribution presented in Table 6. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrates) strategies based on the European Society of Cardiology guidelines.²⁰ QALYs and costs are displayed per person. QALY quality-adjusted life year.

The results of the WTP analysis are presented in Figure 7. In the primary prevention cohort, fibrates were cost-effective across all WTP thresholds, whereas icosapent ethyl reached a 95% probability of cost-effectiveness at a WTP threshold of €30,000. In the secondary prevention cohort, a 95% probability of cost-effectiveness was surpassed

at €19,000 for icosapent ethyl, €47,000 for ezetimibe, €101,000 for fibrates, €116,000 for evolocumab, and €138,000 for alirocumab.

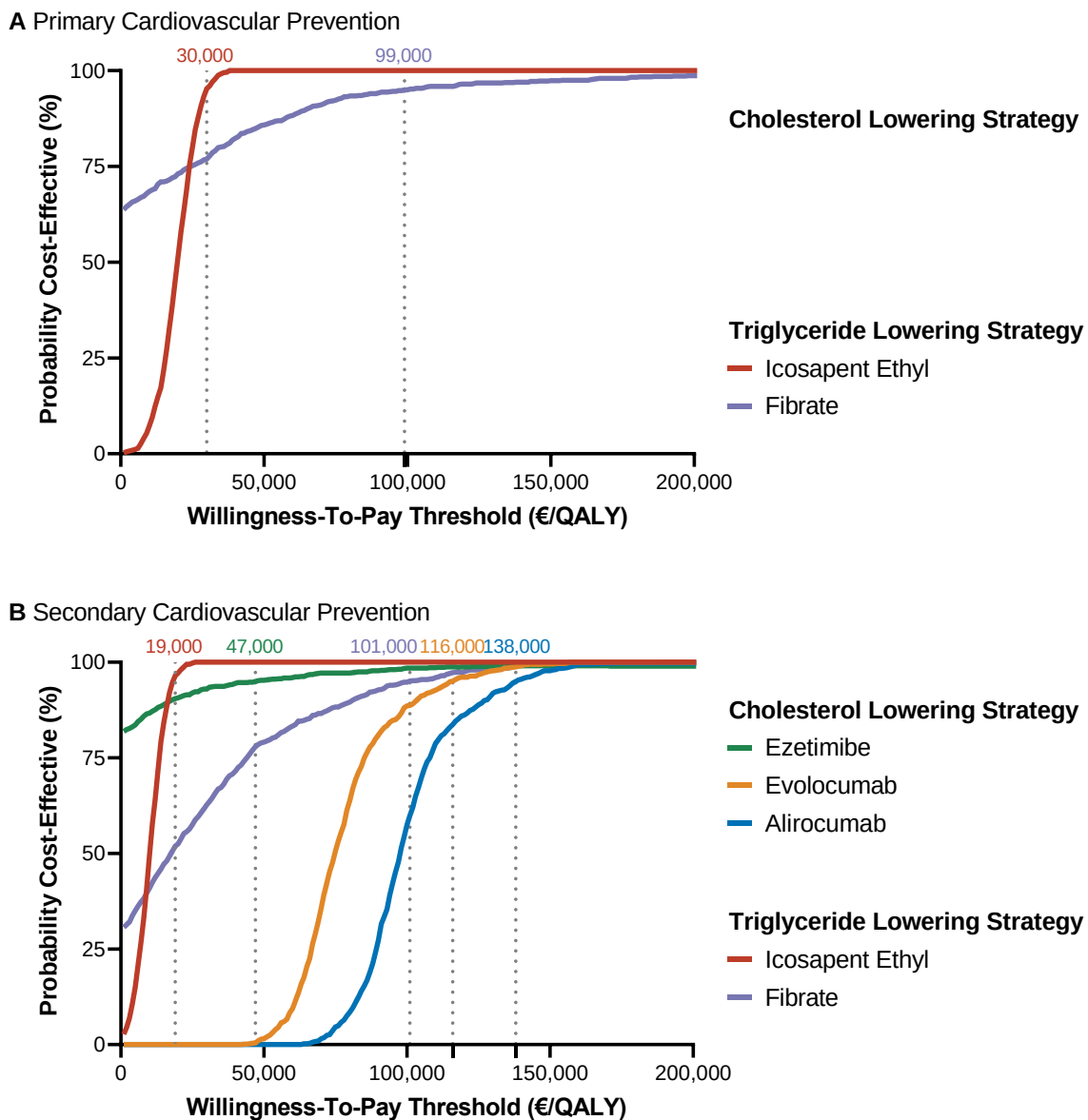


Figure 7: Cost-effectiveness acceptability curves at different willingness-to-pay thresholds for cholesterol- and triglyceride-lowering treatment strategies in combination with statin

Results are visualized for primary (A) and secondary cardiovascular prevention (B). All costs are presented in Euros (€) and inflation-adjusted to 2021 values. The dotted lines present the willingness-to-pay threshold at which the probability of cost-effectiveness surpasses 95%. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines.²⁰ QALY quality-adjusted life year.

Scenario and pricing analyses are enclosed in Table 11 and Figure 8. A 50% discount on list prices reduces evolocumab's and alirocumab's ICER to 13,975 and 40,294 €/QALY, respectively. A 50% premium on icosapent ethyl's list price would yield ICERs of -277 and -6,801 €/QALY for primary and secondary prevention, respectively. Results varied by discount rate and the annual expected CVD risk increase. A lower discount

rate of 0% would result in improved, e.g. lower, ICERs across all evaluated drugs. Assuming a greater annual increase in cardiovascular and non-cardiovascular risks reduced ICERs for all drugs.

Scenario	Primary Prevention		Secondary Prevention				
	Icosapent Ethyl	Fibrate	Icosapent Ethyl	Evolocumab	Alirocumab	Ezetimibe	Fibrate
Annual Treatment Cost							
Base Case	22,352	-74,978	6,851	66,893	91,441	-31,714	16,355
-50%	-277	-76,838	-6,801	13,975	40,294	-38,731	15,415
+50%	44,981	-73,117	20,502	119,810	142,588	-24,697	17,295
Discount rate							
3% (Base Case)	22,352	-74,978	6,851	66,893	91,441	-31,714	16,355
0%	13,098	-89,332	2,857	45,487	75,172	-38,167	23,512
10%	68,990	-52,893	21,152	142,508	146,411	-19,299	4,952

Table 11: Scenario analysis for the incremental cost-effectiveness ratio

ICERs in €/QALY. All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. CVD cardiovascular disease, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year.

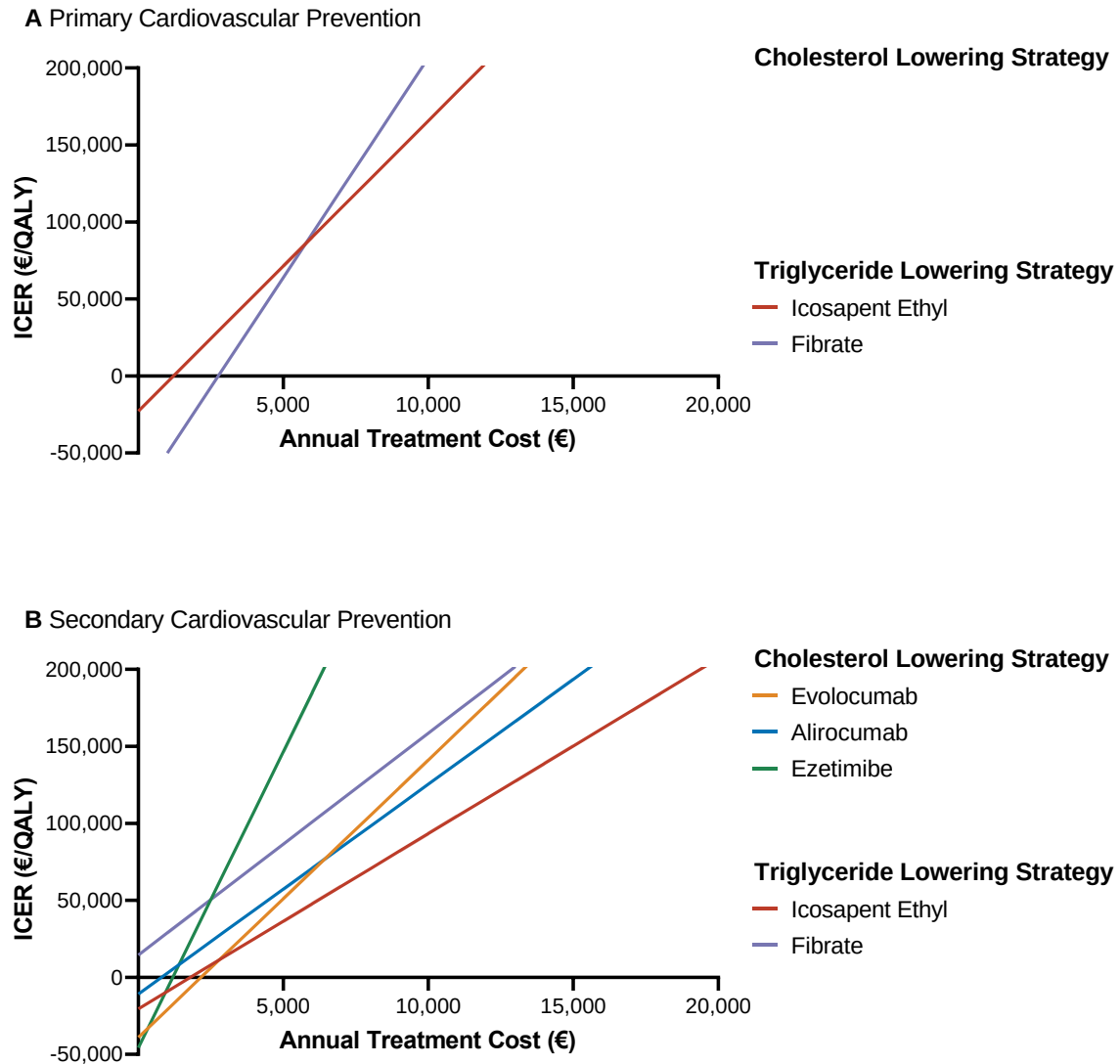


Figure 8: Incremental cost-effectiveness ratios as a function of the annual treatment cost

Results are visualized for primary (A) and secondary cardiovascular prevention (B). All costs are presented in Euros (€) and were inflation-adjusted to 2021 values. Costs and ICER are displayed per person. Treatment options were categorized into cholesterol-lowering (ezetimibe, alirocumab, evolocumab) and triglyceride-lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines.²⁰ ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year.

3.6 Discussion and conclusions

This study evaluated the cost-effectiveness of current lipid-lowering treatment options for primary and secondary cardiovascular prevention from the perspective of the German healthcare system. For primary prevention, results demonstrate that icosapent ethyl plus statin is a cost-effective use of resources (ICER: 22,352 €/QALY). For secondary prevention, ezetimibe (ICER: -39,731 €/QALY), icosapent ethyl (ICER: 6,851 €/QALY), and the PCSK9 inhibitors evolocumab (ICER: 66,893 €/QALY) and alirocumab (ICER: 91,441 €/QALY) increase patient benefit at different economic costs. Fibrates are viable low-cost alternatives to reduce triglyceride levels.

Before patent expiry, ezetimibe was not assessed as cost-effective in the US (ICER: 152,000 USD/QALY).²⁶² However, price reductions caused by genericization improved the cost-effectiveness of ezetimibe (ICER: 81,000 USD/QALY).²⁶³ Studies of ezetimibe conducted in Norway, Finland, Australia, and the UK provide further evidence for the positive benefit-to-expense ratio of ezetimibe in secondary cardiovascular prevention.^{264–267} Nevertheless, ezetimibe's ICER was found to be higher than the WTP thresholds in Thailand and China.^{268,269} Consequently, price reductions caused by generic entry alongside region-specific CVD incidence rates impact the cost-effectiveness of ezetimibe in cardiovascular prevention. In Germany, ezetimibe is available at €156 per year, while both the incidence and the prevalence of CVD remain high.^{241,256} Consequently, the estimated ICER of -39,731 €/QALY for ezetimibe plus statin relative to statin monotherapy is coherent with expectations and previous literature.

Cost-effectiveness evaluations of PCSK9 inhibitors for cardiovascular prevention were previously conducted by scholars and health technology assessment agencies around the world. Initially, PCSK9 inhibitors were frequently assessed as cost-ineffective due to high prices in 2015 (US: ICER of 274,000 USD/QALY at annual treatment costs of USD14,350).^{270,271} However, price discounts to USD5,850 alongside targeted therapy of high-risk patients decreased the ICER to 92,200 USD/QALY by 2020.^{262,272} Our results confirm that evolocumab and alirocumab are not cost-effective at list prices of €5,880 and €7,509, respectively.²⁵⁶ Consequently, Germany's statutory health insurers negotiated discounts, which may vary in magnitude across regions and insurers. Our analysis suggests that price reductions beyond 50% are necessary for PCSK9 inhibitors to reach the cost-effectiveness provided by icosapent ethyl.

The cost-effectiveness of icosapent ethyl was previously assessed in the USA, Canada, Australia, and Japan,^{124,127,128,273–275} after several randomized controlled trials demonstrated the dose-dependent benefits of icosapent ethyl in cardiovascular prevention.^{114,118} In the USA, cost-effectiveness estimates range from 18,000 to 36,118 USD/QALY for primary prevention, depending on model structure and simulation assumptions.^{127,128} For secondary prevention, icosapent ethyl was found to be the dominant treatment strategy compared to the standard of care.¹²⁷ These results are coherent with our findings that icosapent ethyl is cost-effective in primary prevention, but offers even more value to patients and insurers in secondary prevention. However, cost-effectiveness estimates in Australia and Canada are mixed. Although the Canadian Agency for Drugs and Technologies in Health (CADTH) demanded a 43% discount based on an ICER of 105,053 CAD/QALY to reach the Canadian WTP of 50,000 CAD/QALY, other studies estimate an ICER of 42,797 CAD/QALY at a treatment cost of CAD3,557.^{273,274} In Australia, Gao et al. evaluated icosapent ethyl as not cost-effective with an ICER of 59,036 AUD/QALY.²⁷⁵ In contrast, Ademi et al. assessed icosapent ethyl as cost-effective (ICER: 45,036 AUD/QALY), especially for secondary prevention.¹²⁴ Similarly, Koder et al. evaluated eicosapentaenoic acid as cost-effective for secondary, yet not for primary prevention.¹²⁹ Nevertheless, their model derives transition probabilities from the JELIS trial which was conducted 20 years ago in Japan.¹¹² All this shows that the cost-effectiveness of icosapent ethyl is dependent on modeling assumptions alongside drug pricing in regional settings. To the best of our knowledge, this is the first study evaluating the cost-effectiveness of icosapent ethyl in the European context.

Discrepancies in cost-effectiveness ratios for the investigated treatment options are not only driven by differential prices but also distinct efficacies across cardiovascular

event types. While icosapent ethyl, ezetimibe, evolocumab, and alirocumab reduced the risk of MACE by 6% to 25%, the risk reduction was differentially distributed across cardiovascular events with separate costs and disutilities for patients. For instance, the occurrence of non-fatal MI was reduced by 32% (95% CI: 21 to 42) for icosapent ethyl, 28% (95% CI: 19 to 36) for evolocumab, 14% (95% CI: 4 to 23) for alirocumab, and 13% (95% CI: 5 to 20) for ezetimibe. In contrast, the risk reduction for more expensive non-fatal strokes was distributed in a different magnitude and manner: 29% (95% CI: 18 to 40) for icosapent ethyl, 9% (95% CI: -7 to 22) for evolocumab, 27% (95% CI: 7 to 43) for alirocumab, and 14% (95% CI: 0 to 27) for ezetimibe. These distinct efficacies across cardiovascular event types may ultimately explain why alirocumab provides a greater QALY gain than evolocumab even though their observed overall MACE reduction was the same.

3.6.1 Limitations

There are some limitations to our analyses. First, we compared treatment options across clinical trials with different inclusion and exclusion criteria, study sites, and periods. For instance, the ODYSSEY trial includes patients one year after hospitalization for acute coronary syndrome with LDL-C level above 70 mg/dL, whereas the IMPROVE-IT trial restricts the time to 10 days with LDL-C levels above 50 mg/dL. However, we derived distinct transition probabilities from each trial to overcome this limitation.

Second, concerns were raised about the use of mineral oil as a placebo in the REDUCE-IT trial. Consequently, the efficacy of icosapent ethyl could be upward biased and thus overestimate the cost-effectiveness of icosapent ethyl.^{113,120} To account for the potential MACE HR overestimation in the REDUCE-IT trial, transition probabilities in the control arm were lowered by 7% in the present model.²⁵⁸

Third, transition probabilities were derived from clinical trials with time frames ranging from 2.2 to 6.0 years, subsequently annualized, and then extrapolated to a 20-year simulation with annually increasing risks. Our scenario analysis demonstrates that the annual risk increase impacts ICER outcomes.

Fourth, cost-effectiveness ratios were evaluated based on the healthcare system of a single country (Germany). Nevertheless, our model's structure and outcome direction may also inform reimbursement decisions in other European countries, e.g. England, Scotland, Spain, Italy, and the Netherlands.

Fifth, our model neglects side-effects of treatment options, such as injection-site reactions for PCSK9 inhibitors or atrial fibrillation, bleeding, and gastrointestinal pain for icosapent ethyl. Additionally, unobserved discounts on list prices negotiated between statutory insurance funds and manufacturers may impact calculated cost-effectiveness ratios as demonstrated in our pricing analysis.

Sixth, the analyses do not incorporate the differential cardiovascular risk profile across patient cohorts with separate ages and sex. Future studies should conduct similar analyses with a stratification using distinct cardiovascular input parameters for patients with different sex and age profiles.

Finally, our model does not analyse the cost-effectiveness of triple or quadruple lipid-lowering treatment options. For instance, patients may receive combination treatments entailing statins, ezetimibe, fibrates, and icosapent ethyl. From a clinical perspective, it is only warranted to compare within cholesterol-lowering treatment strategy classes and triglyceride-lowering treatment strategy classes, yet no comparison across classes is advised as they are indicated for different patient groups. Further studies are necessary to assess the impact of therapy sequence on clinical efficacy and costs.

3.7 Declarations

Availability of data and materials: Not applicable.

Funding: Open Access funding enabled and organized by Projekt DEAL.

Ethics approval and consent to participate: Not applicable.

Research involving human participants and/or animals: Not applicable.

Consent for publication: Not applicable.

Informed consent: Not applicable.

Competing interests: DM served as an advisor to NB Capital ApS. No other disclosures were reported.

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

4 Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention in the UK

4.1 Abstract

Background: Despite treatment with statins, dyslipidaemia patients with elevated cholesterol and triglyceride levels remain at high residual risk for MACE. New lipid-lowering drugs must prevent the occurrence of MACE and exhibit cost-effectiveness for their successful adoption in 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 the 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 ICER is reported per QALY gained in 2021 Great Britain Pounds (£).

Results: For primary cardiovascular prevention, icosapent ethyl increased QALYs by 0.60 and costs by £7,091 compared to statin monotherapy (ICER = £11,816/QALY). Fenofibrate yielded 0.16 additional QALYs at a cost of £17,942 (ICER = £110,512/QALY). For secondary prevention, the omega-3 fatty acid icosapent ethyl extended QALYs by 0.71 at costs of £6,127 compared to statin monotherapy (ICER = £8,571/QALY). Fenofibrate added 0.28 QALYs at a cost of £2,227 (ICER = £7,876/QALY). Ezetimibe increased QALYs by 0.04 at a cost of -£3,892 (ICER = -£88,807/QALY). PCSK9 inhibitors provided QALYs of 0.34 and 0.57 at costs of £32,797 and £41,433 for evolocumab (ICER = £95,556/QALY) and alirocumab (ICER = £72,829/QALY), respectively. At a willingness-to-pay threshold of £25,000/QALY, there is a probability of 100% for icosapent ethyl (91.4% 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 £2,064 in the UK. For PCSK9 inhibitors, price discounts or prescription restrictions are necessary to achieve cost-effectiveness.

4.2 Key points

- Recently, the triglyceride-lowering omega-3 fatty acid icosapent ethyl and the LDL-C-lowering 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 HDL-C levels (≤ 35 mg/dL or 0.9 mmol/L) for icosapent ethyl.

4.3 Introduction

Every third death is caused by atherosclerosis and resulting CVD in the UK (2018).²⁷⁶ Consequently, there remains a pertinent need to prevent the incidence of CVD and its fatal events such as MI and stroke. The ESC recommends lifestyle modification and subsequently pharmacological therapy to reduce cardiovascular risk factors among high-risk patients, including arterial hypertension, diabetes mellitus, and dyslipidaemia.²⁷⁷ 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 in addition to safety concerns surrounding high statin doses.^{278,279} As a result, additive lipid-lowering therapies have been developed to further reduce the risk of MACE.^{67,102,113,132,243,244}

The ESC categorises additive lipid-modifying drugs according to their primary effect on LDL-C and triglycerides.²⁰ Both indicators function as independent markers to detect at-risk patients.^{82,280} Whilst ezetimibe, evolocumab, and alirocumab predominantly impact LDL-C levels (cholesterol-lowering strategy), icosapent ethyl and fenofibrate mainly lower triglycerides (triglyceride-lowering strategy).^{20,67,102,113,243,244} 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.^{44,113}

Novel pharmacological treatments must demonstrate not only efficacy but also economic value to patients and insurers for successful adoption in clinical practice.²⁷⁷ Public Health England estimates that 6% (£7.4 billion) of the National Health Service's (NHS) annual healthcare budget is spent on CVD,⁴ 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.^{124,127,128,262,273–275} 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.

4.4 Data and methods

4.4.1 Model structure

A Markov model simulating the progression of CVD in dyslipidaemia patients was adapted from existing cost-effectiveness studies (Figure 9).²³ Patients transitioned between three distinct health states: “Alive without CVD”, “Alive with CVD”, and “Dead”. The occurrence 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 with a 3.5% ($\pm$ 1.5%) discount rate.²⁸¹

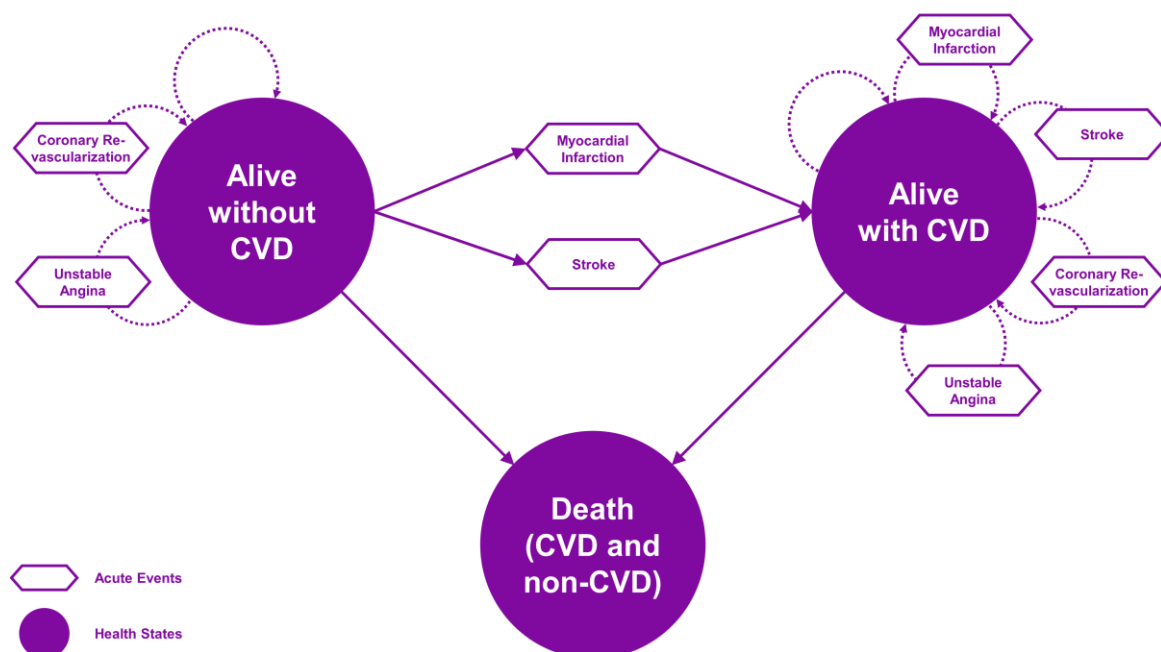


Figure 9: Markov model structure of cardiovascular diseases progression and acute events

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. The model structure was adopted from Michaeli et al.²³ CVD cardiovascular disease.

4.4.2 Evaluated treatment options

For our analyses, we considered all lipid-lowering therapies that were approved by the EMA for primary or secondary cardiovascular prevention after the introduction of statins. Nicotinic acid in combination with laropirant was excluded based on a negative EMA recommendation after the results of the HPS2-THRIVE study in 2013.¹³² For each drug, we selected the largest CVOT in dyslipidaemia patients (Table 12). 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 was no completed CVOT for bile acid sequestrants, inclisiran, bempedoic acid, and other investigational new drugs.

4.4.3 Comparator

The European Society of Cardiology guidelines recommend escalating lipid-lowering treatments from moderate-/high-intensity statins to moderate-/high-intensity statins in combination with an adjunct therapy for patients with refractory elevated blood lipids.²⁰ 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 (Table 12).

	Cholesterol-Lowering Strategy			Triglyceride-Lowering Strategy	
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fenofibrate
Name	IMPROVE-IT ⁶⁷	FOURIER ²⁴³	ODYSSEY ²⁴⁴	REDUCE-IT ¹¹³	ACCORD ¹⁰²
Reference					
Start date	2005	2012	2012	2011	2001
Size	18,144 patients	27,564 patients	18,924 patients	8,179 patients	5,518 patients
Design	Placebo-controlled (1:1)	Placebo-controlled (1:1)	Placebo-controlled (1:1)	Placebo-controlled (1:1)	Placebo-controlled (1:1)
Randomization	Randomized	Randomized	Randomized	Randomized	Randomized
Blinding	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Median age	64 years	63 years	58 years	64 years	62 years
Median follow-up	6 years	2.2 years	2.8 years	4.9 years	4.7 years
Primary endpoint	MACE	MACE	MACE	MACE	MACE
Treatment	10 mg daily (p.o.)	140 mg biweekly or 420 mg monthly (s.c.)	75 mg biweekly (s.c.)	2 g bi-daily (p.o.)	160 mg daily (p.o.)
Baseline therapy	Statin	Statin	Statin	Statin	Statin
Intensity (% patients)	Moderate-Intensity (100%)	High-Intensity (69%), Moderate-Intensity (31%)	High-Intensity (100%)	High-Intensity (31%), Moderate-Intensity (62%), Low-Intensity (6%)	Moderate-Intensity (100%)
Agent (dose per day)	Simvastatin (40 mg)	NR	Atorvastatin (40-80 mg), Rosuvastatin (20-40 mg)	NR	Simvastatin (20-40 mg)

Table 12: Characteristics of cardiovascular outcome trials for lipid-modifying agents

In the FOURIER, ODYSSEY, and REDUCE-IT trials around 3-6% of patients in the treatment and control arms also received ezetimibe in addition to statins. MACE major adverse cardiovascular event, NR not reported, p.o. per oral, s.c. subcutaneous.

4.4.4 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).^{67,102,113,243,244} First, hazard ratios for each acute event, non-CVD death, and CVD death were extracted from the respective trials (Table 13). Second, endpoints were converted to annual transition probabilities using the median follow-up of each CVOT (Table 14), coherent with previous cost-effectiveness studies.^{22,124}

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.^{23,124} For ezetimibe, evolocumab, and alirocumab, CVOT only reported endpoints in patients with established CVD. Therefore, these therapies were only evaluated for the secondary cardiovascular prevention setting. For icosapent ethyl, we accounted for the inappropriate use of the placebo comparator “mineral oil” by reducing transition probabilities in the control arm by 7% as proposed by Doi et al. (2021).^{113,120,258} Similar to previous studies, baseline transition probabilities were multiplied by +10% annually to model the age-dependent increased event and risk rates.

Steen et al. showed that the risk of experiencing a recurrent cardiovascular event after an ACS is substantially higher in the period directly after the ACS.²⁵⁹ In their study of 239,234 US patients, Steen et al. observed an approximately 6-fold greater risk of MACE immediately after patients were hospitalized with an ACS. Consequently, in the present model, MACE transition probabilities were adjusted for this 6-fold risk increase in the period following an ACS.

	Cholesterol-Lowering Strategy			Triglyceride-Lowering Strategy		Distribution	Reference
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fenofibrate		
HAZARD RATIOS							
Alive without CVD (primary prevention)							
Non-fatal MI	a	a	a	0.78 (0.67-0.90)	0.98 (0.84-1.13)	Normal	67,102,113,243,244
CVD death	a	a	a	0.90 (0.77-1.04)	0.92 (0.78-1.06)	Normal	67,102,113,243,244
Non-CVD death	a	a	a	1.14 (0.97-1.31)	1.03 (0.87-1.18)	Normal	67,102,113,243,244
Non-fatal stroke	a	a	a	0.81 (0.69-0.93)	1.13 (0.96-1.29)	Normal	67,102,113,243,244
Hospitalization for unstable angina	a	a	a	0.76 (0.64-0.87)	1.05 (0.89-1.21)	Normal	67,102,113,243,244
Coronary revascularization	a	a	a	0.76 (0.64-0.87)	1.06 (0.90-1.21)	Normal	67,102,113,243,244
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	67,102,113,243,244
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	67,102,113,243,244
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	67,102,113,243,244
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	67,102,113,243,244
Hospitalization 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	67,102,113,243,244
Coronary revascularization	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	67,102,113,243,244
COSTS							
Annual treatment cost	346	4,467	4,412	2,064	141	Fixed	282
Annual statin cost			357			Fixed	282
Alive without CVD			2,497 (±25%)			Gamma	283
Alive with CVD			3,466 (±25%)			Gamma	67,102,113,243,244,283
Non-fatal MI			7,842 (±25%)			Gamma	284,285
Non-fatal stroke			11,512 (±25%)			Gamma	284,285
Hospitalization for unstable angina			3,517 (±25%)			Gamma	283
Coronary revascularization			7,337 (±25%)			Gamma	283
Non-CVD death			2,734 (±25%)			Gamma	286,287
CVD death			6,291 (±25%)			Gamma	284-287
UTILITIES							
Alive without CVD							
65-70 years			0.7395 (0.7385-0.7415)			Beta	288
70+ years			0.6745 (0.6725-0.6770)			Beta	288
Alive with CVD							
65-70 years			0.6595 (0.6585-0.6615)			Beta	247,288
70+ years			0.5945 (0.5925-0.5970)			Beta	247,288
Decrements							
Non-fatal MI			0.04 (0.02-0.05)			Gamma	248
Non-fatal stroke			0.12 (0.09-0.16)			Gamma	248
Hospitalization for unstable angina			0.09 (0.06-0.13)			Gamma	248
Coronary revascularization			0.01 (0.01-0.03)			Gamma	248
OTHERS							
Discount rate			3.5% (2-5)			Fixed	281
Annual risk increase			10%			Fixed	23
Cohort			1,000 patients			Fixed	Assumption
Starting age			63 years			Fixed	67,102,113,243,244
Terminal age			90 years			Fixed	281

Table 13: Input parameters and distribution for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate: hazard ratios, costs, utilities, and others

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 Table 14. Lipid-lowering drugs are presented as cholesterol- and triglyceride-lowering according to guideline recommendations.²⁰ Costs in 2021 Great Britain Pounds (£). CVD Cardiovascular disease, MI Myocardial infarction.

	Icosapent Ethyl		Evolocumab		Alirocumab		Ezetimibe		Fenofibrate	
	Statin + Treat- ment	Statin	Statin + Treat- ment	Statin	Statin + Treat- ment	Statin	Statin + Treat- ment	Statin	Statin + Treat- ment	Statin
Primary Prevention										
Non-fatal MI	0.0121	0.0154	a	a	a	a	a	a	0.0094	0.0096
CVD death	0.0064	0.0071	a	a	a	a	a	a	0.0053	0.0058
Non-CVD death	0.0037	0.0032	a	a	a	a	a	a	0.0056	0.0055
Non-fatal stroke	0.0036	0.0045	a	a	a	a	a	a	0.0027	0.0024
Hospitalization for unstable angina	0.0040	0.0052	a	a	a	a	a	a	0.0081	0.0078
Coronary revascularization	0.0142	0.0187	a	a	a	a	a	a	0.0297	0.0282
Secondary Prevention										
Non-fatal MI	0.0187	0.0274	0.0148	0.0205	0.0244	0.0283	0.0183	0.0212	0.0215	0.0244
CVD death	0.0099	0.0125	0.0084	0.0080	0.0092	0.0104	0.0102	0.0102	0.0120	0.0146
Non-CVD death	0.0056	0.0056	0.0064	0.0062	0.0036	0.0046	0.0130	0.0132	0.0127	0.0137
Non-fatal stroke	0.0055	0.0078	0.0058	0.0064	0.0042	0.0058	0.0055	0.0065	0.0061	0.0060
Hospitalization for unstable angina	0.0061	0.0091	0.0078	0.0080	0.0014	0.0023	0.0029	0.0027	0.0185	0.0196
Coronary revascularization	0.0220	0.0336	0.0257	0.0330	0.0287	0.0327	0.0385	0.0406	0.0727	0.0775

Table 14: Transition probabilities

Hazard ratios were obtained from RCT reporting MACE endpoints for each treatment option to calculate transition probabilities for the incidence of acute cardiovascular events and death: Icosapent ethyl (REDUCE-IT), evolocumab (FOURIER), alirocumab (ODYSSEY), ezetimibe (IMPROVE-IT), and fenofibrate (ACCORD).^{67,102,113,243,244} Adopted from Michaeli et al. (2020).²³ CVD cardiovascular disease, MACE major adverse cardiovascular event, MI myocardial infarction, RCT randomized controlled trial. ^a No clinical trial reporting major cardiovascular adverse events for patients without established CVD was available for ezetimibe, evolocumab, and alirocumab.

4.4.5 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. The model runs for 27 one-year cycles until the patient's age of 90 years.

4.4.6 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 £2,497 per year were based on healthcare expenditure in dyslipidaemia patients without a history of any cardiovascular event.²⁸³ 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 £7,842 for non-fatal MI, £11,512 for non-fatal stroke, £3,517 for unstable angina, and £7,337 for coronary revascularisation.^{284,285} Spending for the "Alive with CVD" state of £3,466 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.^{284,285} Costs for non-CVD deaths were estimated at £2,734 based on the NHS expense during the last 90 days of life weighted by the location of death.^{286,287} The incremental cost of dying from CVD compared to non-CVD causes was estimated at £3,558.²⁸⁵ 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,²⁸² 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.

4.4.7 Utilities

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.²⁸⁸ The HRQoL was reduced by – 0.08 in the “Alive with CVD” state.²⁴⁷ 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.¹²⁴

4.4.8 Outcomes

We calculated the ICER per QALY and LY for each adjunct lipid-lowering drug compared to statin monotherapy. We also contrasted NNT for each cardiovascular event across treatment alternatives.

4.4.9 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, 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 1,000 times from their defined distribution (Table 13) to estimate 90% confidence intervals (CI) for ICERs. Based on the PSA, we estimated the probability that a treatment is cost-effective at the UK's WTP threshold of £20,000 to £30,000 per QALY. Finally, the impact of drug prices on the calculated ICERs was investigated in a pricing analysis.

4.5 Results

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

4.5.1 Base case analysis

4.5.2 Cholesterol-lowering strategy

Figure 10 visualises the results of base case ICERs per QALY gained on a cost-effectiveness plane. Ezetimibe increased QALYs gained by 0.04 at cost reductions of -£3,892 compared to statin monotherapy for secondary cardiovascular prevention (ICER = -£88,807 per QALY). PCSK9 inhibitors provided incremental QALYs of 0.34 and 0.57 at costs of £32,797 and £41,433 for evolocumab (ICER = £95,556 per QALY) and alirocumab (ICER = £72,829 per QALY), respectively. Incremental LYs gained were 0.37 for ezetimibe, 0.94 for evolocumab, and 1.31 for alirocumab (Figure 11).

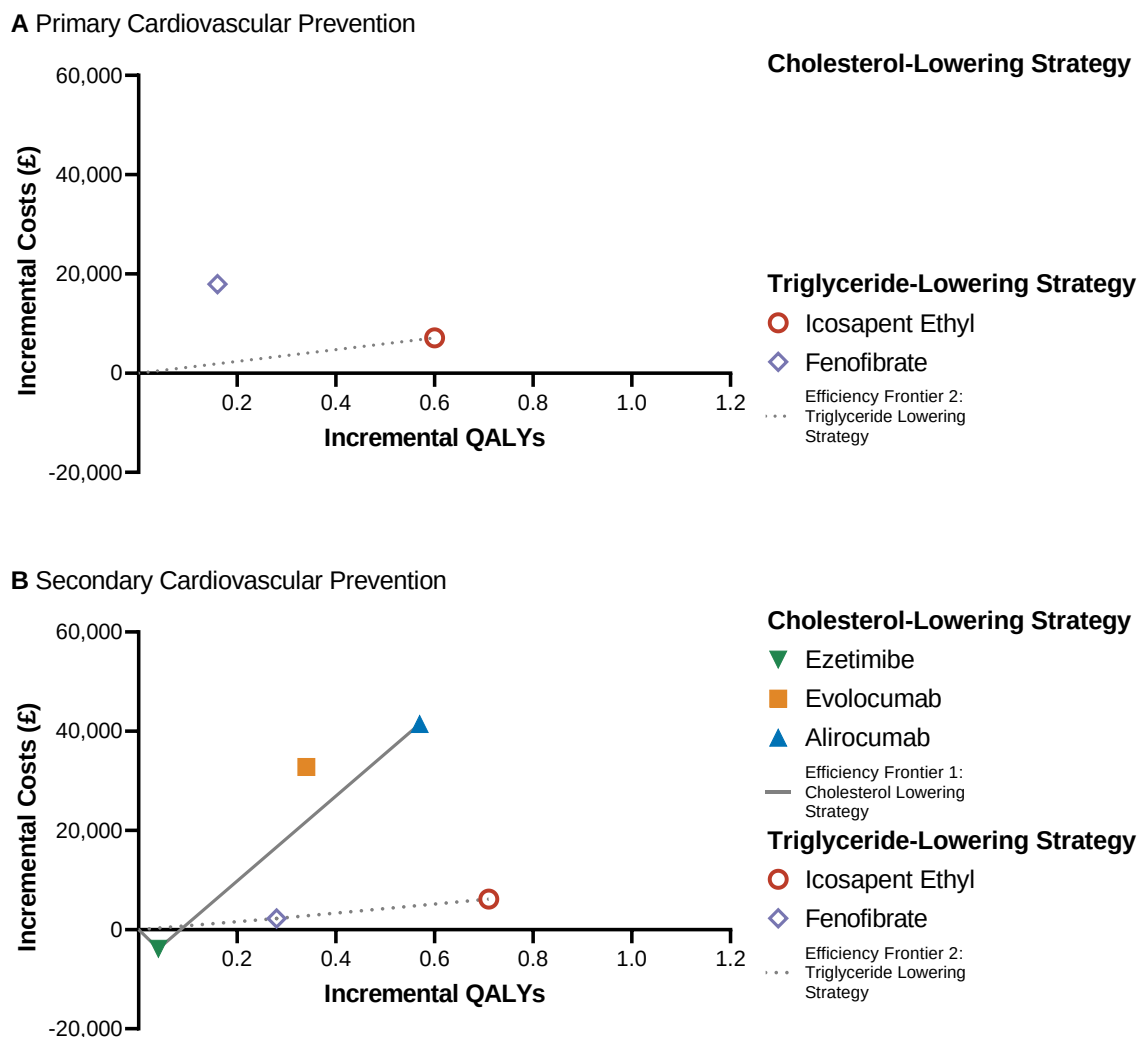


Figure 10: Cost-effectiveness plane for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (A) and secondary (B) cardiovascular prevention

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.²⁰ Costs in 2021 Great Britain Pounds (£). QALY quality-adjusted life year.

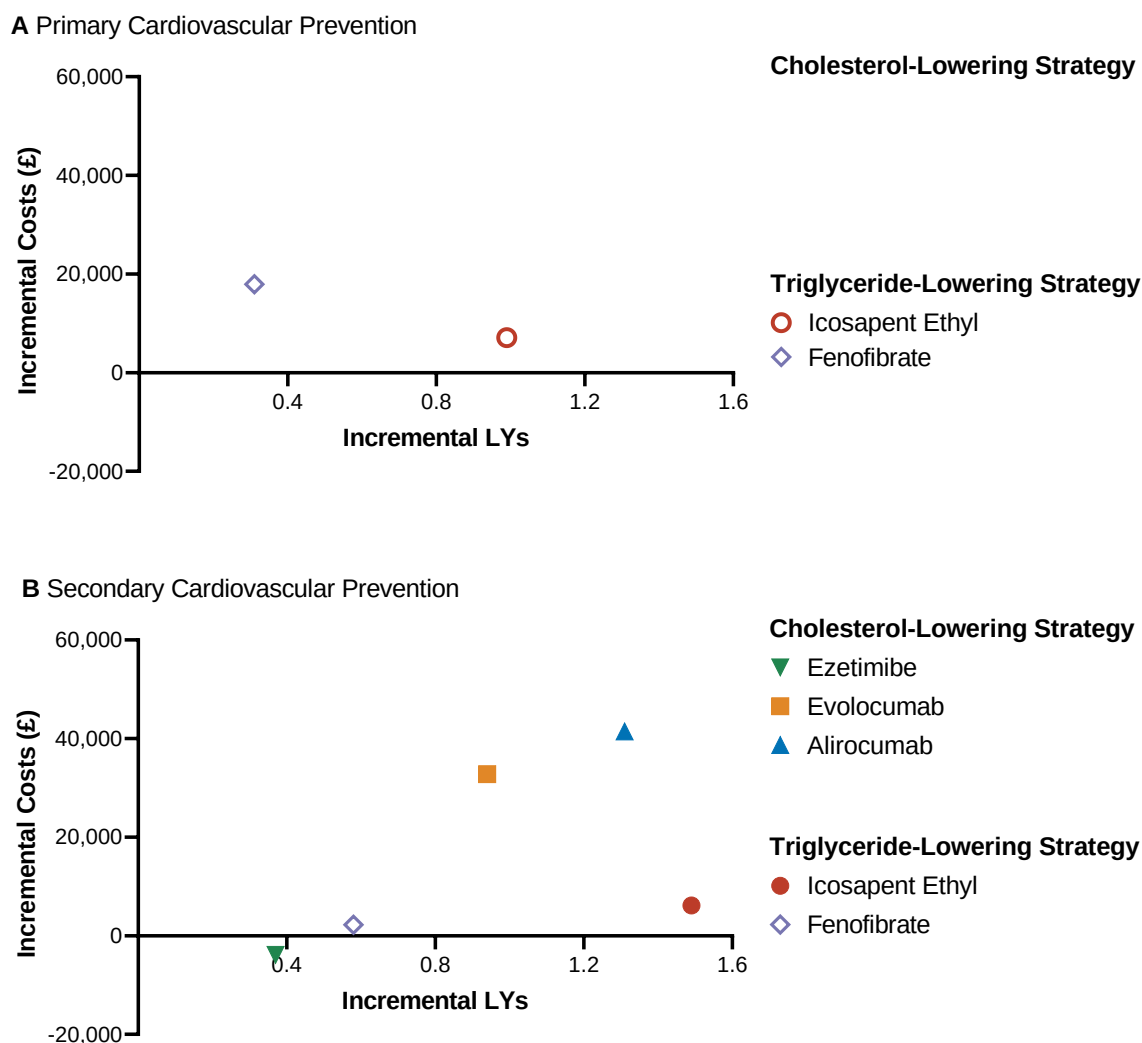


Figure 11: Cost-effectiveness plane for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (A) and secondary (B) cardiovascular prevention by life years gained

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.²⁰ Costs in 2021 Great Britain Pounds (£). LY life year.

4.5.3 Triglyceride-lowering strategy

Regarding primary prevention, icosapent ethyl increased QALYs by 0.60 and costs by £7,091 compared to statin monotherapy (ICER = £11,816 per QALY). Fenofibrate yielded 0.31 additional QALYs at incremental costs of £17,942 (ICER = £110,512 per QALY). Figure 11 demonstrates that icosapent ethyl provided greater LYs gained than fenofibrate (0.99 vs 0.31).

In secondary prevention, icosapent ethyl extended QALYs by 0.71 for patients at costs of £6,127 compared to statin monotherapy (ICER = £8,571 per QALY). Fenofibrate added 0.58 QALYs at costs of £2,227 (ICER = £7,876 per QALY). LYs 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 15).

	Cholesterol-Lowering Strategy			Triglyceride-Lowering Strategy	
	Ezetimibe	Evolocumab	Alirocumab	Icosapent Ethyl	Fenofibrate
Primary Prevention					
Incremental LYs	a	a	a	0.99	0.31
Incremental QALYs	a	a	a	0.60	0.16
Incremental costs (£)	a	a	a	7,091	17,942
ICER (£ per LY)	a	a	a	7,197	57,790
ICER (£ per QALY)	a	a	a	11,816	110,512
Number needed to treat (NNT)					
Non-fatal MI	a	a	a	1.4	-3.3
Non-fatal stroke	a	a	a	5.0	-7.9
Hospitalization for unstable angina	a	a	a	3.9	-3.1
Coronary revascularization	a	a	a	1.1	-0.8
Death	a	a	a	1.7	-3.3
Secondary Prevention					
Incremental LYs	0.37	0.94	1.31	1.49	0.58
Incremental QALYs	0.04	0.34	0.57	0.71	0.28
Incremental costs (£)	-3,892	32,797	41,433	6,127	2,227
ICER (£ per LY)	-10,463	34,902	31,618	4,120	3,810
ICER (£ per QALY)	-88,807	95,556	72,829	8,571	7,876
Number needed to treat (NNT)					
Non-fatal MI	4.0	1.5	48.6	2.9	-14.2
Non-fatal stroke	12.5	9.3	14.8	12.0	-16.4
Hospitalization for unstable angina	-41153	12.4	21.1	7.8	-8.3
Coronary revascularization	3.7	1.1	-55.4	2.1	-2.1
Death	19.6	12.4	51.3	14.2	-338

Table 15: Base case LYs, QALYs, ICERs, and NNT for primary and secondary cardiovascular prevention

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 the age of 90 years. Lipid-lowering drugs are presented as cholesterol- and triglyceride-lowering according to guideline recommendations.²⁰ Costs in 2021 Great Britain Pounds (£). *QALY* quality-adjusted life year, *LY* life year, *ICER* incremental cost-effectiveness ratio, *NNT* number needed to treat, *CVD* cardiovascular disease, *MI* myocardial infarction, *NA* not applicable. ^a No clinical trials reporting major cardiovascular adverse events for patients without established CVD were available for ezetimibe, evolocumab, and alirocumab.

4.5.4 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.

4.5.5 Univariate sensitivity and scenario analyses

Univariate sensitivity analysis demonstrates that ICERs are mainly influenced by the transition probabilities to cardiovascular events (Table 16 and Table 17). The scenario analysis in Table 18 shows the influence of variations in the underlying discount rate and estimated annual risk increase on ICERs.

	Icosapent ethyl		Fenofibrate	
	Lower CI	Upper CI	Lower CI	Upper CI
Cost alive with CVD	11,194	12,438	110,484	110,540
Cost alive without CVD	11,242	12,389	109,346	111,678
Cost coronary revascularization	10,486	13,146	102,298	118,726
Cost CVD death	5,231	18,400	99,520	121,504
Cost hospitalization for unstable angina	11,644	11,988	109,503	111,521
Cost non-CVD death	11,370	12,261	110,107	110,917
Cost non-fatal MI	10,746	12,886	108,441	112,583
Cost non-fatal stroke	11,399	12,233	109,176	111,848
TP alive with CVD to coronary revascularization	11,816	20,998	-41,972	110,512
TP alive with CVD to CVD death	11,816	21,494	59,435	205,728
TP alive with CVD to hospitalization for unstable angina	11,816	20,867	-118,306	110,512
TP alive with CVD to non-CVD death	11,500	12,125	106,563	114,421
TP alive with CVD to non-fatal MI	11,816	19,448	-112,123	110,512
TP alive with CVD to non-fatal stroke	11,387	12,248	105,972	115,258
TP alive without CVD to coronary revascularization	11,222	12,411	106,266	114,817
TP alive without CVD to CVD death	9,673	14,767	79,913	171,264
TP alive without CVD to hospitalization for unstable angina	11,713	11,919	108,720	112,348
TP alive without CVD to non-CVD death	11,396	12,319	82,357	168,623
TP alive without CVD to non-fatal MI	11,816	17,592	36,434	334,608
TP alive without CVD to non-fatal stroke	10,418	13,285	81,918	149,162
Utility alive with CVD (+75 years)	11,741	11,876	110,393	110,607
Utility alive with CVD (≤ 74 years)	11,794	11,859	110,468	110,600
Utility alive without CVD (+75 years)	11,790	11,837	110,002	110,923
Utility alive without CVD (≤ 74 years)	11,815	11,816	110,506	110,515
Utility coronary revascularization	11,689	11,881	106,898	118,470
Utility hospitalization for unstable angina	11,725	11,892	106,491	115,788
Utility non-fatal MI	11,724	11,887	109,243	112,207
Utility non-fatal stroke	11,744	11,863	109,129	112,714

Table 16: Univariate sensitivity analysis for primary cardiovascular prevention

Results were displayed for icosapent ethyl and fenofibrate. The table visualizes the variation of input parameters on ICERs by their confidence intervals presented in Table 13. Costs in 2021 Great Britain Pounds (£). CVD cardiovascular disease, ICER incremental cost-effectiveness ratio, MI myocardial infarction, TP transition probability.

	Ezetimibe		Evolocumab		Alirocumab		Icosapent ethyl		Fenofibrate	
	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI
TP alive with CVD to CVD death	-102,806	-83,146	94,461	97,822	94,461	97,822	5,902	12,502	-10,845	40,041
Cost coronary revascularization	-88,928	-88,661	94,959	96,152	94,959	96,152	1,874	8,571	-15,078	48,664
Cost CVD death	-104,867	-74,538	95,366	95,745	95,366	95,745	6,624	10,803	4,296	776,223
Cost hospitalization for unstable angina	-88,844	-88,771	92,252	98,374	92,252	98,374	2,621	17,439	6,085	9,667
Cost non-CVD death	-92,168	-82,807	94,828	96,283	94,828	96,283	3,094	14,047	7,855	7,917
Cost non-fatal MI	-99,837	-82,340	94,744	96,239	94,744	96,239	7,465	9,677	7,785	7,950
Cost non-fatal stroke	-92,205	-84,032	95,556	111,489	95,556	111,489	7,707	9,435	7,703	8,048
TP alive with CVD to coronary revascularization	-93,135	-83,748	92,884	96,959	92,884	96,959	6,769	10,373	7,642	8,109
TP alive with CVD to CVD death	-89,668	-87,767	93,183	97,928	93,183	97,928	8,176	8,966	7,453	8,299
TP alive with CVD to hospitalization for unstable angina	-88,807	19,961	87,874	103,238	87,874	103,238	7,856	9,296	7,866	7,888
TP alive with CVD to non-CVD death	-90,611	-87,004	92,869	98,242	92,869	98,242	8,246	8,896	7,659	8,092
TP alive with CVD to non-fatal MI	-92,692	-84,923	74,936	164,792	74,936	164,792	7,823	9,210	7,844	7,925
TP alive with CVD to non-fatal stroke	-88,807	-4,918	92,039	99,072	92,039	99,072	8,430	8,712	6,759	8,661
TP alive without CVD to coronary revascularization	-97,089	-80,525	94,550	96,219	94,550	96,219	8,517	8,616	6,195	9,611
TP alive without CVD to CVD death	-97,667	-79,947	89,567	128,835	89,567	128,835	8,517	8,613	7,808	7,960
TP alive without CVD to hospitalization for unstable angina	-96,162	-81,453	92,631	98,571	92,631	98,571	8,494	8,610	7,816	7,997
TP alive without CVD to non-CVD death	-117,945	-59,669	93,719	97,018	93,719	97,018	8,433	8,684	6,016	9,736
TP alive without CVD to non-fatal MI	-88,807	41,100	81,786	116,475	81,786	116,475	8,530	8,597	4,098	11,654
TP alive without CVD to non-fatal stroke	-88,807	99,051	76,922	187,433	76,922	187,433	8,533	8,648	7,876	80,242

Table 17: Univariate sensitivity analysis for secondary cardiovascular prevention

Results were displayed for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate. The table visualizes the variation of input parameters on ICERs by their confidence intervals presented in Table 13. Costs in 2021 Great Britain Pounds (£). CVD cardiovascular disease, ICER incremental cost-effectiveness ratio, MI myocardial infarct, TP transition probability.

Scenario	Primary Prevention		Secondary Prevention				
	Icosapent Ethyl	Fenofibrate	Icosapent Ethyl	Evolocumab	Alirocumab	Ezetimibe	Fenofibrate
Annual treatment cost							
Base case	11,816	110,512	8,571	95,556	72,829	-88,807	7,876
-50%	-9,664	106,039	-6,773	24,600	30,932	-124,975	6,143
+50%	33,296	114,985	23,915	166,512	114,727	-52,639	9,608
Discount rate							
3.5% (Base case)	11,816	110,512	8,571	95,556	72,829	-88,807	7,876
2.0%	5,947	120,398	6,115	77,371	65,000	-83,693	8,790
5.0%	18,773	102,012	11,359	117,955	81,788	-96,208	6,989

Table 18: Scenario analysis

ICER (£ per QALY) are presented under different modelling scenarios. Costs in 2021 Great Britain Pounds (£). CVD cardiovascular disease, ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year.

4.5.6 Subgroup analyses

All drugs displayed differential efficacy outcomes in their clinical trials. Consequently, ICERs were assessed for a variety of patient populations (Table 19). Compared to the overall population, icosapent ethyl was especially cost-effective among patients aged < 65 years for both primary (ICER = £11,331 per QALY) and secondary (ICER = £3,663 per QALY) cardiovascular prevention. Details of these Markov models simulations can be found in Appendix Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, and Table 28. 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 = £4,593 per QALY) and secondary (ICER = £3,116 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 = £56,648 per QALY) and alirocumab (ICER = £63,337 per QALY). ICERs were lower for icosapent ethyl and PCSK9 inhibitors in patients with a baseline hsCRP lower than ≤ 2 mg/L.

Subgroup	Primary Prevention	Secondary Prevention		
	Icosapent Ethyl	Icosapent Ethyl	Evolocumab	Alirocumab
Base case	11,816	8,571	95,556	72,829
Age				
<65 years	11,331	3,663	109,075	110,050
≥ 65 years	109,277	20,317	95,556	54,036
Baseline triglyceride ≥ 200 mg/dl and HDL-C ≤ 35 mg/dl ^a				
No	26,518	7,137	NR	NR
Yes	4,593	3,116	NR	NR
Baseline LDL-C ≥ 100 mg/dl ^b				
No	NR	NR	271,130	135,503
Yes	NR	NR	56,648	52,651
Baseline hsCRP				
≤ 2 mg/l	6,710	4,752	74,056	63,337
> 2 mg/l	40,713	12,390	181,445	110,050

Table 19: Subgroup analysis

ICERs (£ per QALY) are presented for different patient populations. Costs in 2021 Great Britain Pounds (£). CVD cardiovascular disease, HDL-C high-density-lipoprotein-cholesterol, hsCRP high-sensitivity C-reactive protein, 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. An HDL-C level of 35 mg/dL is equivalent to 0.9 mmol/L. ^b A LDL-C level of 100 mg/dL is equivalent to 2.6 mmol/L.

4.5.7 Probabilistic sensitivity analyses

Input parameters were drawn from their defined distribution across CIs displayed in Table 13 for 1,000 iterations. Incremental QALYs and costs of these 1,000 resamples are visualised on a cost-effectiveness plane in Figure 12.

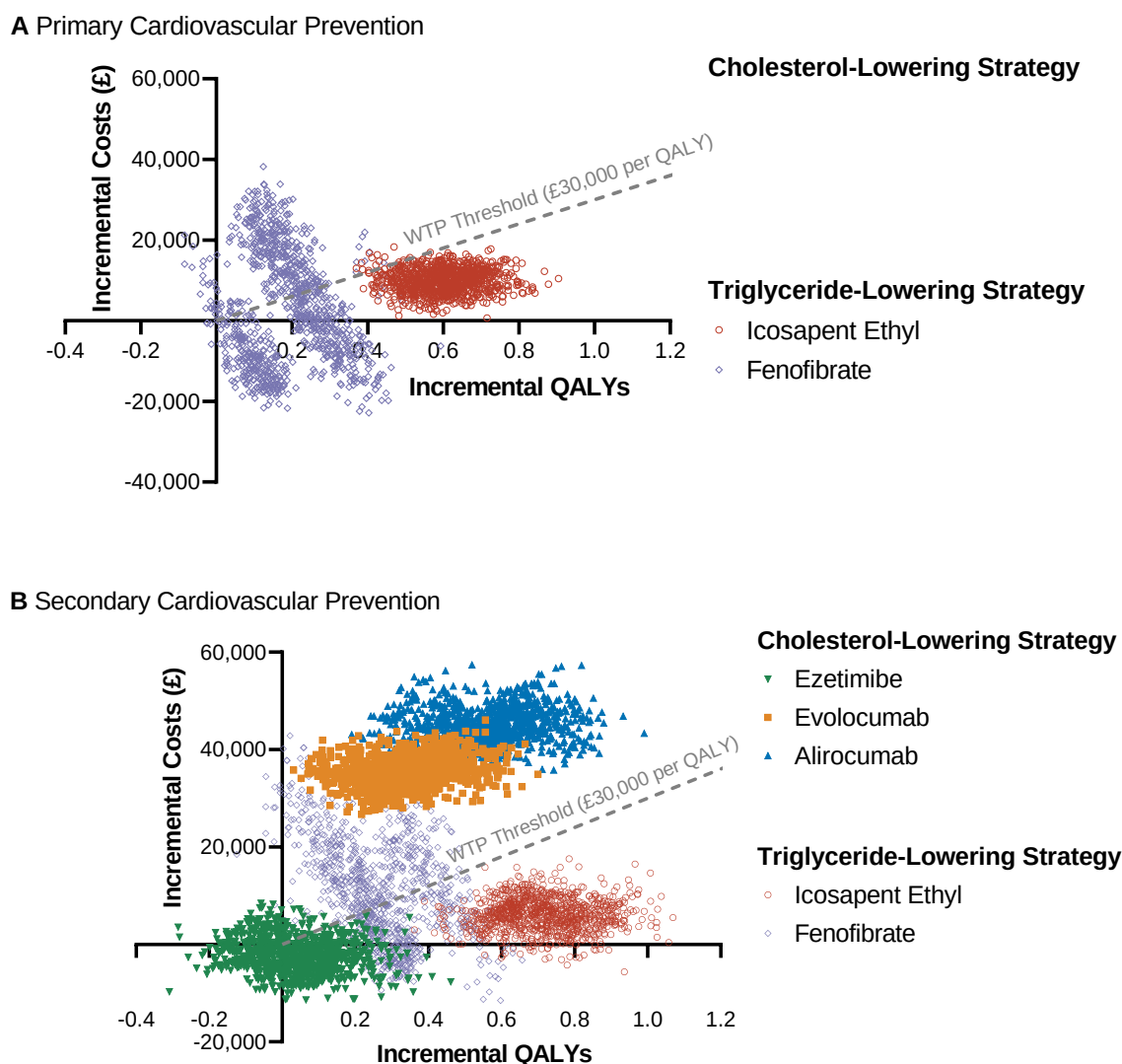


Figure 12: Probabilistic sensitivity analysis for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (A) and secondary (B) cardiovascular prevention

Input parameters displayed in Table 13 were varied by their confidence intervals and distribution; 1,000 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.²⁰ 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

For the cholesterol-lowering strategy, QALYs gained were higher for alirocumab (0.57, 95% CI 0.34 to 0.78) than for evolocumab (0.35, 95% CI 0.15 to 0.54) and ezetimibe (0.04, 95% CI -0.14 to 0.23) in secondary prevention. The ICER of alirocumab and

evolocumab remained robust at £84,1093 (95% CI 57,060 to 139,544) and £120,253 per QALY (95% CI 65,644 to 234,992), respectively.

For the triglyceride-lowering strategy, QALY gains were consistently higher for icosapent ethyl (0.60, 95% CI 0.46 to 0.74) than fenofibrate (0.19, 95% CI 0.03 to 0.38, $p < 0.001$) in patients without established CVD. For secondary prevention, icosapent ethyl offered QALY gains of 0.72 (95% CI 0.54 to 0.91) compared to 0.27 (95% CI 0.05 to 0.49) for fenofibrate. The ICER of icosapent ethyl remained robust at £16,835 per QALY (95% CI 8,266 to 26,378) for primary prevention and at £8,761 per QALY (95% CI 834 to 17,505) for secondary prevention.

4.5.8 Willingness-to-pay and pricing analyses

In primary prevention, fenofibrate was cost-effective across all WTP thresholds (Figure 13). Icosapent ethyl surpassed a 90% probability of cost-effectiveness at a WTP of £25,000 per QALY. Assuming a WTP of the National Institute for Health and Care Excellence of £25,000 per QALY, icosapent ethyl was cost-effective 91.4% of times – at a WTP of £30,000 per QALY, icosapent ethyl was cost-effective 98.6% of simulations for primary prevention. We estimated a maximum list price of £2,937 for icosapent ethyl to maintain cost-effectiveness, representing a +42% premium to the list price of £2,064 proposed by the manufacturer (Figure 14).

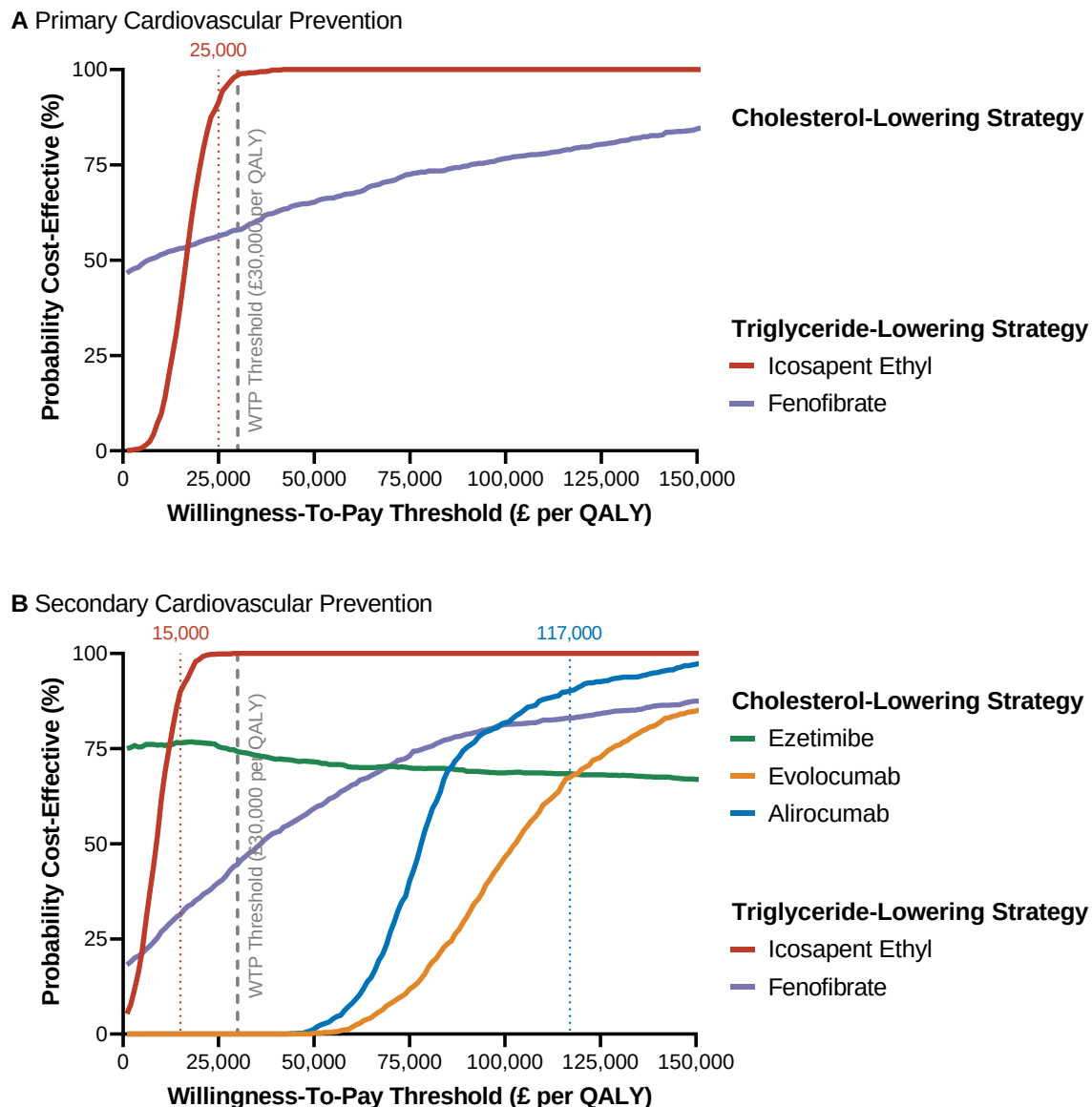


Figure 13: Probability of cost-effectiveness at different willingness-to-pay thresholds for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (A) and secondary (B) cardiovascular prevention

The grey line illustrates the English NHS' upper willingness-to-pay threshold of £30,000 per QALY. The dotted lines show the willingness-to-pay thresholds at which the probability of cost-effectiveness surpasses 90%. Lipid-lowering drugs are presented as cholesterol- and triglyceride-lowering according to guideline recommendations.²⁰ 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.

In secondary prevention, the generic drugs ezetimibe and fenofibrate were cost-effective compared to statin monotherapy across all WTP thresholds. Icosapent ethyl surpassed a 90% probability of cost-effectiveness at a WTP threshold of £15,000 per QALY, alirocumab at a threshold of £117,000 per QALY, and evolocumab at a threshold of £179,000 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 £3,505 for icosapent ethyl, which represents a +70% increase compared to

manufacturer guidance. In contrast, in the UK, discounts of -46% to -51% are necessary to achieve cost-effectiveness for alirocumab and evolocumab respectively.

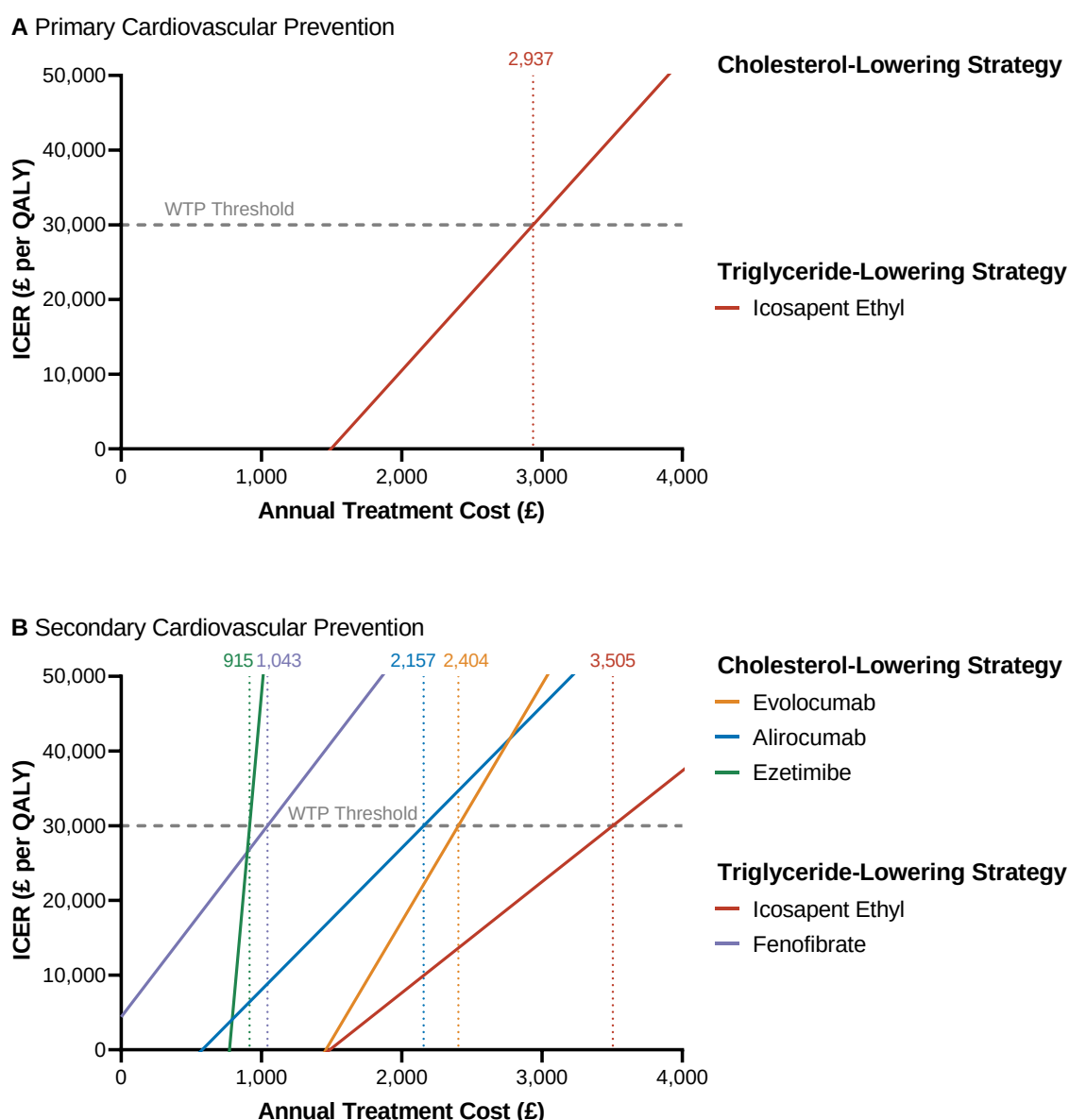


Figure 14: Incremental cost-effectiveness ratios as a function of the annual treatment cost at a willingness-to-pay threshold of £30,000 per QALY

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.²⁰ In graph A, fenofibrate is not shown due to estimated treatment costs beyond £100,000. Costs in 2021 Great Britain Pounds (£). ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year.

4.6 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 could be cost-effective for secondary prevention, whilst the PCSK9 inhibitors evolocumab and alirocumab are not. Price discounts beyond -46% 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, the triglyceride-lowering drug icosapent ethyl is cost-effective for patients with and without established CVD at the UK's WTP of £25,000 per QALY. Fenofibrate could be cost-effective depending on the underlying modelling assumptions.

4.6.1 Cholesterol-lowering strategy

PCSK9 inhibitors reduce the risk of MACE by -15%, in contrast to an observed risk reduction of -6% provided by ezetimibe.^{67,243,244} However, PCSK9 inhibitors are costly with list prices of around £4,400 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.

Consistent with our results, the NHS concluded that both PCSK9 inhibitors are not cost-effective at annual treatment costs of around £4,400.^{289,290} The committee demanded discounts of undisclosed magnitude alongside prescribing restrictions. Our analyses suggest that discounts beyond -46% are necessary for PCSK9 inhibitors 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). ICERs can be substantially lowered by reducing prices and restricting prescription to at-risk patients as analyses in the USA demonstrate.^{262,272} Similarly, our subgroup analysis demonstrates lower ICERs among patients with baseline LDL-C levels of ≥ 100 mg/dL for evolocumab (ICER = £56,648 per QALY) and alirocumab (ICER = £52,651 per QALY).

In line with our results, meta-analyses reviewing the cost-effectiveness of lipid-lowering therapeutics across the globe concluded that ezetimibe could be cost-effective, in contrast to PCSK9 inhibitors, which are not cost-effective.^{22,264,291,292} Only one of ten studies (10%) evaluated PCSK9 inhibitors as cost-effective, compared to five out of eight (63%) for ezetimibe.²² Previous studies required discounts of -20% to -88% on PCSK9 inhibitors' list prices to achieve cost-effectiveness.²⁹² Although the clinical economics of PCSK9 inhibitors are well established in developed nations, evidence from low-income countries is scarce.²⁹³

4.6.2 Triglyceride-lowering strategy

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.^{112,113,118} Informed by these CVOT, studies evaluated the cost-effectiveness of icosapent ethyl in Germany, the USA, Australia, Canada, and Japan.^{23,124,127,128,273–275}

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.^{127,128} Ademi et al. considered icosapent

ethyl cost-effective at the Australian WTP threshold of AUD50,000 per QALY, especially for secondary prevention.¹²⁴ They calculated an ICER of AUD45,036 per QALY using a Markov model simulation based on annual treatment costs of AUD1,637. In contrast, Gao et al. calculated an ICER of AUD59,036 per QALY based on annual treatment costs of AUD3,768.²⁷⁵

Similar to Australia, icosapent ethyl's clinical economics remains disputed in Canada. Lachaine et al. calculated an ICER of CAD42,797 per QALY, whilst the 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.^{273,274} Kodera et al. assessed icosapent ethyl as cost-effective for primary, yet not secondary prevention in Japan.¹²⁹ 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 EPA per day.^{112,129} 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.¹¹⁸

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 = £8,571 per QALY). Furthermore, the conducted subgroup analysis demonstrates that 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, one might expect negative, e.g. cost saving ICERs for fenofibrate. However, fenofibrate's clinical efficacy and its role in primary and secondary cardiovascular prevention remain disputed as previously described in chapter 1. Consequently, the reported large uncertainty in HRs and derived transition probabilities led to wide variations in the ICERs for fenofibrate in the probabilistic sensitivity analysis.

4.6.3 Limitations

First, long-term efficacy data are not available for all considered lipid-lowering drugs. We therefore derived annual transition probabilities from the aforementioned CVOT with follow-up periods between 2.2 and 6.0 years (Table 12), 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,^{22,124} 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%.^{113,120} To account for the potential MACE HR overestimation in the REDUCE-IT trial, transition probabilities in the control arm were lowered by 7% in this model.²⁵⁸ Icosapent ethyl's efficacy is underlined by the FDA and EMA regulatory approval.

Our analyses were conducted from the perspective of the UK's 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.^{102,113}

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.²⁹⁴

The analyses do not incorporate the differential cardiovascular risk profile across patient cohorts with separate age and sex profiles. Future studies should conduct similar analyses with a stratification using distinct cardiovascular input parameters for patients with different sex and age profiles. Furthermore, the scenario analysis by age, triglyceride, HDL-C, LDL-C and hsCRP were based on subgroup analyses reported in the underlying CVOT trials. However, subgroup analyses from RCTs are often subject to spurious results.^{295–297} Moreover, only the REDUCE-IT trial reported significant results for the age subgroup analysis. Therefore, the results of the presented scenario analysis must be cautiously reviewed in light of potentially spurious input parameters for the Markov simulation and shall not be over-interpreted.

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.

4.6.4 Future research

Coherent with previous meta-analyses,^{78,88} 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 hypercholesterolemia. This strategy permits companies to finance costly CVOT, which requires 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 for 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.^{298,299} 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.²⁹⁴ 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.

4.7 Conclusion

Icosapent ethyl in combination with statins is cost-effective for primary and secondary cardiovascular prevention at an annual price of £2,064 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 of around £4,400, PCSK9 inhibitors are not cost-effective for secondary prevention. Cost-effectiveness can be achieved with price discounts of -46% to -51% 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, at low economic cost that could even be cost-saving for the healthcare system, depending on the evaluated patient population.

4.8 Declarations

Funding: Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest: DM served as an advisor to NB Capital ApS. No other disclosures were reported.

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

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

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6 Appendix

Region	Deaths	DALYs	Incidence	Prevalence
Afghanistan	-59%	-55%	-43%	-38.3%
Albania	134%	88%	114%	110.6%
Algeria	11%	-9%	42%	52.2%
American Samoa	65%	44%	67%	68.7%
Andorra	70%	20%	30%	41.0%
Angola	-26%	-32%	-7%	1.0%
Antigua and Barbuda	-19%	-14%	18%	21.2%
Argentina	-24%	-34%	-8%	9.6%
Armenia	43%	23%	52%	59.3%
Australia	-31%	-43%	10%	29.4%
Austria	-28%	-39%	3%	16.1%
Azerbaijan	30%	25%	32%	28.8%
Bahamas	33%	27%	52%	48.5%
Bahrain	-39%	-40%	82%	81.4%
Bangladesh	61%	36%	75%	81.0%
Barbados	-9%	-7%	36%	34.8%
Belarus	39%	28%	36%	37.2%
Belgium	-26%	-39%	-10%	8.8%
Belize	-10%	-1%	27%	34.9%
Benin	-26%	-24%	-5%	2.1%
Bermuda	-8%	-25%	70%	71.4%
Bhutan	70%	30%	62%	71.9%
Bolivia (Plurinational State of)	3%	-15%	16%	26.4%
Bosnia and Herzegovina	87%	47%	97%	103.9%
Botswana	16%	14%	16%	24.2%
Brazil	1%	-13%	27%	41.6%
Brunei Darussalam	-5%	-10%	30%	47.7%
Bulgaria	42%	17%	25%	37.3%
Burkina Faso	0%	-4%	-5%	-2.5%
Burundi	-42%	-41%	-14%	-5.3%
C�te d'Ivoire	3%	-7%	13%	16.9%
Cabo Verde	21%	11%	11%	19.7%
Cambodia	36%	12%	41%	52.1%
Cameroon	-8%	-6%	5%	11.0%
Canada	-17%	-27%	1%	16.7%
Central African Republic	-16%	-15%	-1%	0.7%
Chad	-31%	-26%	-15%	-11.9%
Chile	-1%	-12%	40%	53.7%
China	57%	27%	94%	99.7%
Colombia	18%	-8%	55%	69.7%
Comoros	13%	1%	13%	25.4%
Congo	-20%	-25%	0%	7.5%
Cook Islands	46%	25%	98%	106.8%
Costa Rica	24%	14%	52%	57.2%
Croatia	6%	-15%	25%	44.2%
Cuba	28%	12%	42%	47.1%
Cyprus	-27%	-34%	8%	22.7%
Czechia	-30%	-41%	6%	34.6%
Democratic People's Republic of Korea	81%	54%	65%	60.1%
Democratic Republic of the Congo	-13%	-20%	-3%	0.6%
Denmark	-49%	-55%	-18%	-7.8%
Djibouti	49%	29%	31%	43.3%
Dominica	1%	1%	31%	31.0%
Dominican Republic	112%	80%	58%	54.6%
Ecuador	21%	3%	32%	38.2%
Egypt	-5%	-23%	23%	25.2%
El Salvador	30%	-4%	44%	53.3%
Equatorial Guinea	-59%	-63%	-27%	-8.6%
Eritrea	4%	-8%	1%	13.4%
Estonia	-11%	-29%	34%	51.9%
Eswatini	28%	25%	22%	27.5%
Ethiopia	-39%	-50%	-2%	11.6%
Fiji	34%	20%	59%	63.8%
Finland	-7%	-29%	5%	20.8%
France	-16%	-29%	-1%	12.6%
Gabon	-20%	-22%	1%	8.1%
Gambia	39%	20%	17%	19.7%
Georgia	25%	3%	26%	46.6%
Germany	-24%	-37%	-17%	11.0%
Ghana	18%	9%	20%	22.4%
Greece	23%	0%	11%	24.4%
Greenland	11%	-5%	39%	50.9%
Grenada	-36%	-24%	20%	25.7%
Guam	76%	54%	94%	97.8%
Guatemala	-2%	-22%	20%	35.1%
Guinea	-16%	-18%	-4%	-0.6%
Guinea-Bissau	-17%	-19%	-2%	3.4%
Guyana	4%	0%	35%	39.5%
Haiti	-18%	-25%	5%	8.9%
Honduras	62%	29%	25%	33.3%
Hungary	-8%	-25%	11%	26.0%
Iceland	-30%	-40%	4%	16.8%
India	32%	14%	48%	54.1%
Indonesia	67%	47%	57%	61.3%
Iran (Islamic Republic of)	35%	3%	76%	77.4%
Iraq	-10%	-13%	10%	17.8%
Ireland	-46%	-53%	-13%	5.6%
Israel	-47%	-56%	-12%	4.3%
Italy	-2%	-23%	9%	27.8%
Jamaica	14%	8%	46%	45.1%
Japan	30%	3%	39%	53.9%
Jordan	-16%	-18%	40%	46.2%
Kazakhstan	3%	1%	4%	13.3%
Kenya	22%	21%	11%	21.7%
Kiribati	-6%	-8%	12%	14.9%
Kuwait	11%	2%	69%	65.3%
Kyrgyzstan	-7%	-11%	-5%	-3.7%
Lao People's Democratic Republic	4%	-4%	6%	13.9%
Latvia	13%	-4%	36%	53.7%
Lebanon	17%	-3%	45%	47.4%
Lesotho	37%	43%	14%	18.2%
Liberia	-41%	-41%	-16%	-7.7%
Libya	36%	6%	73%	71.8%
Lithuania	34%	12%	45%	58.7%
Luxembourg	-51%	-58%	-16%	-2.4%
Madagascar	-18%	-19%	-2%	5.3%
Malawi	-16%	-24%	0%	5.2%
Malaysia	18%	11%	34%	45.2%
Maldives	-27%	-44%	19%	39.1%
Mali	-29%	-32%	-12%	-7.3%
Malta	-5%	-21%	31%	47.7%
Marshall Islands	49%	58%	48%	55.4%
Mauritania	-32%	-38%	-1%	6.9%
Mauritius	-7%	-19%	51%	68.9%
Mexico	58%	38%	49%	55.3%
Micronesia (Federated States of)	38%	34%	31%	37.8%

Monaco	-35%	-40%	-12%	-7.1%
Mongolia	5%	12%	20%	32.1%
Montenegro	69%	52%	55%	54.8%
Morocco	42%	24%	49%	50.5%
Mozambique	-10%	-10%	-6%	-3.5%
Myanmar	7%	-11%	24%	34.7%
Namibia	-2%	-10%	-2%	6.7%
Nauru	1%	6%	8%	8.2%
Nepal	38%	13%	39%	43.5%
Netherlands	-28%	-38%	2%	19.3%
New Zealand	-19%	-35%	2%	24.0%
Nicaragua	76%	42%	36%	47.4%
Niger	-21%	-29%	-2%	0.9%
Nigeria	-42%	-40%	-11%	-0.1%
Niue	7%	12%	34%	38.3%
North Macedonia	41%	26%	48%	54.2%
Northern Mariana Islands	156%	100%	138%	142.4%
Norway	-52%	-58%	-17%	-4.2%
Oman	-39%	-43%	21%	24.5%
Pakistan	0%	10%	5%	3.6%
Palau	53%	53%	83%	81.2%
Palestine	-28%	-26%	11%	16.9%
Panama	3%	-8%	35%	41.4%
Papua New Guinea	15%	13%	8%	10.7%
Paraguay	15%	9%	24%	34.1%
Peru	-13%	-29%	30%	43.8%
Philippines	152%	158%	38%	43.7%
Poland	-12%	-28%	3%	38.9%
Portugal	-22%	-38%	-4%	21.9%
Puerto Rico	12%	-5%	82%	95.2%
Qatar	-53%	-49%	25%	24.0%
Republic of Korea	-25%	-45%	35%	79.5%
Republic of Moldova	35%	19%	50%	61.2%
Romania	34%	10%	33%	57.5%
Russian Federation	16%	7%	26%	36.7%
Rwanda	-36%	-43%	-10%	8.1%
Saint Kitts and Nevis	-48%	-43%	12%	15.9%
Saint Lucia	11%	6%	62%	64.4%
Saint Vincent and the Grenadines	34%	29%	69%	65.8%
Samoa	17%	13%	22%	25.6%
San Marino	23%	1%	4%	12.2%
Sao Tome and Principe	2%	-2%	5%	12.8%
Saudi Arabia	1%	18%	53%	51.9%
Senegal	1%	-8%	8%	13.4%
Serbia	29%	8%	36%	48.4%
Seychelles	-15%	-10%	27%	29.9%
Sierra Leone	-28%	-26%	-11%	-6.3%
Singapore	-28%	-37%	26%	46.4%
Slovakia	-10%	-22%	15%	33.9%
Slovenia	-13%	-30%	39%	54.0%
Solomon Islands	18%	16%	13%	15.5%
Somalia	-22%	-24%	-7%	-1.3%
South Africa	28%	7%	19%	21.8%
South Sudan	-27%	-27%	1%	5.9%
Spain	-11%	-29%	-1%	14.4%
Sri Lanka	22%	7%	63%	77.6%
Sudan	-29%	-36%	-2%	6.7%
Suriname	10%	8%	49%	49.2%
Sweden	-35%	-43%	-14%	2.0%
Switzerland	-28%	-41%	-7%	6.0%
Syrian Arab Republic	43%	17%	86%	88.0%
Taiwan (Province of China)	14%	-2%	80%	102.6%
Tajikistan	8%	14%	2%	0.3%
Thailand	47%	26%	75%	96.2%
Timor-Leste	131%	84%	49%	55.0%
Togo	17%	11%	21%	25.5%
Tokelau	-6%	-5%	15%	20.6%
Tonga	41%	23%	27%	29.5%
Trinidad and Tobago	10%	1%	60%	63.8%
Tunisia	63%	36%	83%	85.9%
Turkey	13%	-10%	42%	49.7%
Turkmenistan	38%	36%	43%	48.1%
Tuvalu	3%	-6%	17%	22.0%
Uganda	-18%	-18%	-5%	3.1%
Ukraine	53%	49%	35%	30.7%
United Arab Emirates	13%	24%	78%	76.9%
United Kingdom	-45%	-51%	-19%	-8.3%
United Republic of Tanzania	-6%	-15%	6%	13.6%
United States of America	-16%	-19%	-9%	11.3%
United States Virgin Islands	119%	84%	115%	116.4%
Uruguay	-20%	-32%	3%	8.6%
Uzbekistan	35%	56%	32%	24.0%
Vanuatu	44%	38%	22%	25.9%
Venezuela (Bolivarian Republic of)	59%	38%	62%	72.4%
Viet Nam	36%	32%	66%	69.9%
Yemen	-4%	-13%	14%	21.6%
Zambia	1%	-7%	-3%	5.4%
Zimbabwe	35%	37%	21%	17.6%

Table 20: Percentage change in cardiovascular disease epidemiology around the globe from 1990 to 2019

Data from the GBD study (2019).² DALY disability-adjusted life year, GBD Global Burden of Diseases.

WITH ICOSAPENT ETHYL															
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	
0	1000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	991	11	3	4	13	6	3	0	0	0	0	0	0	0	0
2	967	12	4	4	14	12	7	14	0	0	0	0	0	0	0
3	941	13	4	4	15	19	11	29	0	0	0	0	0	0	0
4	914	13	4	4	16	26	15	45	1	0	0	1	1	0	0
5	884	14	4	5	17	34	19	61	1	0	0	1	1	1	1
6	853	15	5	5	18	42	24	78	2	0	1	2	3	1	1
7	819	16	5	5	19	50	29	96	3	1	1	3	4	2	2
8	784	17	5	6	20	60	34	113	4	1	1	5	7	3	3
9	746	18	5	6	21	69	40	131	5	1	2	6	10	4	4
10	707	19	6	6	22	79	45	149	7	1	2	8	14	6	6
11	666	20	6	6	23	90	51	166	9	2	3	10	19	8	8
12	623	20	6	7	24	101	58	183	11	2	4	13	25	10	10
13	579	21	6	7	25	112	64	198	14	3	4	16	34	13	13
14	534	21	6	7	25	123	71	212	15	3	5	18	44	17	17
15	487	22	7	7	26	135	77	223	17	4	6	20	56	21	21
16	441	22	7	7	26	147	84	232	20	4	6	23	71	26	26
17	394	22	7	7	26	158	90	237	22	5	7	26	89	31	31
18	348	21	6	7	25	170	97	238	24	5	8	28	110	38	38
19	303	21	6	7	24	181	103	235	26	6	8	31	134	45	45
20	259	20	6	7	23	192	109	227	27	6	9	32	161	53	53
21	217	19	6	6	22	202	115	214	28	6	9	33	191	61	61
22	179	17	5	6	20	211	120	196	28	7	9	33	225	70	70
23	143	16	5	5	18	219	125	174	28	7	9	33	260	79	79
24	111	14	4	5	16	226	129	149	26	6	9	31	297	87	87
25	83	12	4	4	14	233	133	122	24	6	8	28	333	96	96
26	60	10	3	3	11	238	136	94	21	5	7	24	368	104	104
27	41	8	2	3	9	242	138	68	17	5	6	20	400	111	111
WITHOUT ICOSAPENT ETHYL															
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	
0	1000	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	990	14	4	5	17	7	3	0	0	0	0	0	0	0	0
2	961	16	5	5	19	14	6	18	0	0	0	0	0	0	0
3	930	17	5	6	20	22	10	38	1	0	0	1	0	0	0
4	897	18	5	6	22	30	13	58	2	0	1	2	1	0	0
5	862	19	5	6	23	38	17	79	3	1	1	3	3	1	1
6	824	20	6	7	24	48	22	100	4	1	1	5	5	2	2
7	784	21	6	7	25	57	26	122	6	1	2	7	8	3	3
8	743	22	6	7	27	67	30	143	8	2	3	10	13	4	4
9	699	23	7	8	28	78	35	163	11	2	4	14	18	5	5
10	654	24	7	8	29	89	40	183	13	3	4	16	26	8	8
11	608	24	7	8	29	100	45	201	16	3	5	19	36	10	10
12	560	25	7	8	30	112	50	217	19	4	6	23	48	13	13
13	511	25	7	9	31	123	56	230	22	4	7	27	64	17	17
14	462	25	7	9	31	135	61	239	25	5	8	30	82	21	21
15	412	25	7	9	30	147	66	244	28	6	9	34	104	26	26
16	363	25	7	8	30	158	71	245	30	6	10	37	130	32	32
17	316	24	7	8	29	169	76	240	32	7	11	40	161	38	38
18	270	23	7	8	28	180	81	229	34	7	11	41	195	45	45
19	226	21	6	7	26	190	86	214	34	8	12	42	233	53	53
20	185	20	6	7	24	199	90	192	34	8	11	42	274	60	60
21	148	18	5	6	22	207	93	167	33	8	11	40	317	68	68
22	114	16	5	5	19	214	97	139	30	7	10	37	360	76	76
23	85	13	4	5	16	220	99	109	26	6	9	32	403	83	83
24	61	11	3	4	13	225	102	81	22	6	7	27	442	89	89
25	41	9	2	3	10	229	104	55	17	5	6	21	477	94	94
26	26	6	2	2	8	232	105	34	13	3	4	16	505	98	98
27	15	4	1	1	5	234	106	22	6	2	2	8	522	101	101

Table 21: Markov Model primary prevention cohort with and without icosapent ethyl (under 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. “Alive without CVD”, “Alive with CVD”, “CVD death”, and “Non-CVD death” represent health states. “MI”, “Stroke”, “Hospitalization for unstable angina pectoris”, and “Coronary revascularization” represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH ICOSAPENT ETHYL															
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION						
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	
0	1000		0	0	0	0	0	0	0	0	0	0	0	0	0
1	987	16	5	5	19	9	5	0	0	0	0	0	0	0	0
2	951	17	5	6	20	18	10	21	0	0	0	0	0	0	0
3	913	18	6	6	22	28	16	43	1	0	0	1	0	0	0
4	873	20	6	6	23	38	22	65	2	0	1	2	2	1	1
5	830	21	6	7	24	49	28	88	3	1	1	3	3	1	1
6	785	21	6	7	25	61	35	111	5	1	1	5	6	2	2
7	739	22	7	7	26	72	41	133	6	1	2	8	10	4	4
8	690	23	7	8	27	85	48	155	9	2	3	10	16	6	6
9	641	24	7	8	28	97	56	175	12	2	4	14	23	9	9
10	589	24	7	8	28	110	63	193	13	3	4	16	32	12	12
11	537	25	7	8	29	123	70	209	16	3	5	19	44	16	16
12	485	25	7	8	29	137	78	222	19	4	6	22	58	20	20
13	432	24	7	8	29	150	85	231	21	5	7	25	76	26	26
14	381	24	7	8	28	162	93	235	24	5	8	28	97	32	32
15	330	23	7	8	27	175	100	235	26	6	8	31	121	40	40
16	281	22	7	7	26	187	107	229	28	6	9	33	150	47	47
17	235	21	6	7	24	198	113	217	29	7	9	34	181	56	56
18	192	19	6	6	22	208	119	200	29	7	10	34	216	65	65
19	153	17	5	6	20	217	124	178	29	7	9	34	254	75	75
20	118	15	4	5	18	225	128	152	27	7	9	32	292	84	84
21	88	13	4	4	15	232	132	124	25	6	8	29	331	93	93
22	63	10	3	3	12	237	136	95	21	6	7	25	368	101	101
23	42	8	2	3	10	242	138	68	18	5	6	21	402	108	108
24	26	6	2	2	7	245	140	45	13	4	4	16	430	114	114
25	15	4	1	1	5	247	141	26	9	3	3	11	453	118	118
26	7	3	1	1	3	249	142	12	6	2	2	7	468	121	121
27	3	1	0	0	2	249	142	7	2	1	1	3	476	123	123
WITHOUT ICOSAPENT ETHYL															
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION						
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	
0	1000		0	0	0	0	0	0	0	0	0	0	0	0	0
1	987	19	6	6	23	9	4	0	0	0	0	0	0	0	0
2	949	21	6	7	25	18	8	24	0	0	0	0	0	0	0
3	907	22	6	7	27	29	13	50	1	0	0	1	1	0	0
4	864	23	7	8	28	39	18	76	3	1	1	3	2	1	1
5	818	24	7	8	29	50	23	102	5	1	2	6	5	2	2
6	770	25	7	9	30	62	28	128	8	1	3	9	9	3	3
7	721	26	8	9	32	74	33	152	10	2	3	12	16	4	4
8	669	27	8	9	32	86	39	175	13	3	4	16	24	7	7
9	616	27	8	9	33	99	45	196	16	3	5	20	35	9	9
10	563	28	8	9	34	112	50	214	20	4	7	24	48	13	13
11	508	28	8	9	34	125	56	228	23	5	8	28	66	17	17
12	454	28	8	9	34	138	62	238	26	5	9	32	87	22	22
13	400	27	8	9	33	150	68	242	29	6	10	36	112	27	27
14	348	26	8	9	32	162	73	241	32	7	11	39	142	33	33
15	297	25	7	9	31	174	79	233	34	7	11	42	177	40	40
16	249	24	7	8	29	185	83	220	35	8	12	43	216	48	48
17	204	22	6	7	26	195	88	200	35	8	12	43	258	56	56
18	162	20	6	7	24	204	92	175	34	8	11	41	303	64	64
19	126	17	5	6	21	212	96	147	31	7	11	38	348	72	72
20	94	15	4	5	18	219	99	116	28	7	9	34	393	79	79
21	67	12	3	4	15	224	101	86	23	6	8	29	435	86	86
22	45	9	3	3	11	229	103	59	19	5	6	23	472	92	92
23	28	7	2	2	8	232	105	36	14	4	5	17	503	96	96
24	16	5	1	2	6	234	106	24	7	2	2	9	521	99	99
25	8	3	1	1	4	236	106	14	5	1	2	6	536	101	101
26	3	2	0	1	2	236	107	7	3	1	1	3	545	103	103
27	0	1	0	0	1	237	107	3	1	0	0	2	550	104	104

Table 22: Markov Model primary prevention cohort with and without icosapent ethyl (over 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. "Alive without CVD", "Alive with CVD", "CVD death", and "Non-CVD death" represent health states. "MI", "Stroke", "Hospitalization for unstable angina pectoris", and "Coronary revascularization" represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH ICOSAPENT ETHYL																
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION								
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	981	19	6	6	22	13	6	6
2	0	0	0	0	0	0	0	0	962	25	6	8	29	26	12	12
3	0	0	0	0	0	0	0	0	941	27	6	9	32	41	19	19
4	0	0	0	0	0	0	0	0	918	29	7	10	35	57	26	26
5	0	0	0	0	0	0	0	0	892	32	7	10	38	74	33	33
6	0	0	0	0	0	0	0	0	865	35	7	11	41	94	41	41
7	0	0	0	0	0	0	0	0	835	38	8	12	45	115	50	50
8	0	0	0	0	0	0	0	0	803	41	8	13	49	138	59	59
9	0	0	0	0	0	0	0	0	768	45	9	15	52	163	69	69
10	0	0	0	0	0	0	0	0	730	48	9	16	56	190	80	80
11	0	0	0	0	0	0	0	0	690	51	10	17	61	219	90	90
12	0	0	0	0	0	0	0	0	647	55	10	18	64	251	102	102
13	0	0	0	0	0	0	0	0	602	52	10	17	61	285	114	114
14	0	0	0	0	0	0	0	0	554	52	10	17	61	320	126	126
15	0	0	0	0	0	0	0	0	504	51	10	17	60	358	138	138
16	0	0	0	0	0	0	0	0	453	50	10	16	59	397	150	150
17	0	0	0	0	0	0	0	0	400	48	10	16	56	437	162	162
18	0	0	0	0	0	0	0	0	347	45	10	15	53	478	174	174
19	0	0	0	0	0	0	0	0	295	42	9	14	49	519	186	186
20	0	0	0	0	0	0	0	0	244	38	8	12	44	559	197	197
21	0	0	0	0	0	0	0	0	196	33	7	11	39	598	207	207
22	0	0	0	0	0	0	0	0	151	28	7	9	33	633	216	216
23	0	0	0	0	0	0	0	0	111	23	5	7	27	665	223	223
24	0	0	0	0	0	0	0	0	77	18	4	6	21	693	230	230
25	0	0	0	0	0	0	0	0	50	13	3	4	16	715	235	235
26	0	0	0	0	0	0	0	0	29	9	2	3	11	732	238	238
27	0	0	0	0	0	0	0	0	15	6	2	2	7	744	241	241

WITHOUT ICOSAPENT ETHYL																
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION								
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	978	25	7	8	31	16	6	6
2	0	0	0	0	0	0	0	0	956	36	7	12	44	33	11	11
3	0	0	0	0	0	0	0	0	932	39	8	13	47	51	17	17
4	0	0	0	0	0	0	0	0	905	42	8	14	52	71	24	24
5	0	0	0	0	0	0	0	0	876	46	9	15	56	93	31	31
6	0	0	0	0	0	0	0	0	844	50	9	17	62	118	38	38
7	0	0	0	0	0	0	0	0	810	55	10	18	67	144	46	46
8	0	0	0	0	0	0	0	0	773	59	10	20	72	173	54	54
9	0	0	0	0	0	0	0	0	732	64	11	21	78	204	63	63
10	0	0	0	0	0	0	0	0	689	61	11	20	75	238	72	72
11	0	0	0	0	0	0	0	0	644	62	11	21	76	275	82	82
12	0	0	0	0	0	0	0	0	595	62	12	21	76	313	92	92
13	0	0	0	0	0	0	0	0	544	61	12	21	75	354	102	102
14	0	0	0	0	0	0	0	0	491	60	12	20	74	397	112	112
15	0	0	0	0	0	0	0	0	436	58	11	19	71	442	122	122
16	0	0	0	0	0	0	0	0	380	55	11	18	67	488	132	132
17	0	0	0	0	0	0	0	0	325	51	10	17	63	533	142	142
18	0	0	0	0	0	0	0	0	271	46	10	16	57	579	151	151
19	0	0	0	0	0	0	0	0	219	41	9	14	50	622	159	159
20	0	0	0	0	0	0	0	0	170	35	8	12	43	663	167	167
21	0	0	0	0	0	0	0	0	127	29	6	10	35	700	174	174
22	0	0	0	0	0	0	0	0	89	23	5	8	28	732	179	179
23	0	0	0	0	0	0	0	0	59	17	4	6	21	758	183	183
24	0	0	0	0	0	0	0	0	35	12	3	4	14	778	187	187
25	0	0	0	0	0	0	0	0	19	7	2	2	9	793	189	189
26	0	0	0	0	0	0	0	0	8	4	1	1	5	802	190	190
27	0	0	0	0	0	0	0	0	4	2	0	1	2	805	191	191

Table 23: Markov Model secondary prevention cohort with and without icosapent ethyl (under 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. “Alive without CVD”, “Alive with CVD”, “CVD death”, and “Non-CVD death” represent health states. “MI”, “Stroke”, “Hospitalization for unstable angina pectoris”, and “Coronary revascularization” represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH ICOSAPENT ETHYL																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	969	29	9	9	34	22	9	
2	0	0	0	0	0	0	0	0	937	41	8	13	49	44	19	
3	0	0	0	0	0	0	0	0	902	44	9	14	52	69	29	
4	0	0	0	0	0	0	0	0	865	48	9	16	57	96	39	
5	0	0	0	0	0	0	0	0	825	52	10	17	61	125	50	
6	0	0	0	0	0	0	0	0	781	56	10	18	66	156	62	
7	0	0	0	0	0	0	0	0	735	59	11	19	70	190	75	
8	0	0	0	0	0	0	0	0	686	57	11	18	67	227	87	
9	0	0	0	0	0	0	0	0	634	57	11	19	68	265	100	
10	0	0	0	0	0	0	0	0	580	57	11	18	67	306	114	
11	0	0	0	0	0	0	0	0	524	56	11	18	66	349	127	
12	0	0	0	0	0	0	0	0	466	54	11	17	64	393	141	
13	0	0	0	0	0	0	0	0	407	51	11	17	61	438	154	
14	0	0	0	0	0	0	0	0	349	48	10	16	56	484	167	
15	0	0	0	0	0	0	0	0	292	44	9	14	52	529	180	
16	0	0	0	0	0	0	0	0	237	39	9	13	46	572	191	
17	0	0	0	0	0	0	0	0	186	33	8	11	39	613	201	
18	0	0	0	0	0	0	0	0	140	28	6	9	33	650	210	
19	0	0	0	0	0	0	0	0	100	22	5	7	26	682	218	
20	0	0	0	0	0	0	0	0	66	17	4	5	20	709	224	
21	0	0	0	0	0	0	0	0	41	12	3	4	14	731	229	
22	0	0	0	0	0	0	0	0	22	8	2	2	9	746	232	
23	0	0	0	0	0	0	0	0	10	4	1	1	5	756	234	
24	0	0	0	0	0	0	0	0	4	2	1	1	3	761	235	
25	0	0	0	0	0	0	0	0	1	1	0	0	1	763	235	
26	0	0	0	0	0	0	0	0	0	0	0	0	0	764	235	
27	0	0	0	0	0	0	0	0	0	0	0	0	0	764	236	

WITHOUT ICOSAPENT ETHYL																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	969	34	10	11	41	23	8	
2	0	0	0	0	0	0	0	0	938	50	9	17	62	47	15	
3	0	0	0	0	0	0	0	0	904	54	10	18	66	73	23	
4	0	0	0	0	0	0	0	0	867	58	11	20	72	101	31	
5	0	0	0	0	0	0	0	0	827	63	11	21	77	132	40	
6	0	0	0	0	0	0	0	0	785	68	11	23	83	166	50	
7	0	0	0	0	0	0	0	0	738	65	12	22	80	202	60	
8	0	0	0	0	0	0	0	0	689	66	12	22	81	241	70	
9	0	0	0	0	0	0	0	0	637	66	12	22	81	282	80	
10	0	0	0	0	0	0	0	0	583	66	12	22	81	326	91	
11	0	0	0	0	0	0	0	0	526	64	12	22	79	372	102	
12	0	0	0	0	0	0	0	0	467	62	12	21	76	420	113	
13	0	0	0	0	0	0	0	0	408	59	12	20	72	469	123	
14	0	0	0	0	0	0	0	0	348	55	11	18	67	518	134	
15	0	0	0	0	0	0	0	0	290	50	10	17	61	567	144	
16	0	0	0	0	0	0	0	0	234	44	9	15	54	613	153	
17	0	0	0	0	0	0	0	0	182	37	8	13	46	657	161	
18	0	0	0	0	0	0	0	0	136	31	7	10	38	696	168	
19	0	0	0	0	0	0	0	0	96	24	6	8	30	731	174	
20	0	0	0	0	0	0	0	0	63	18	4	6	22	759	178	
21	0	0	0	0	0	0	0	0	38	12	3	4	15	780	182	
22	0	0	0	0	0	0	0	0	20	8	2	3	10	796	184	
23	0	0	0	0	0	0	0	0	9	4	1	1	5	805	186	
24	0	0	0	0	0	0	0	0	4	2	0	1	2	810	186	
25	0	0	0	0	0	0	0	0	1	1	0	0	1	812	187	
26	0	0	0	0	0	0	0	0	0	0	0	0	0	813	187	
27	0	0	0	0	0	0	0	0	0	0	0	0	0	813	187	

Table 24: Markov Model secondary prevention cohort with and without icosapent ethyl (over 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. "Alive without CVD", "Alive with CVD", "CVD death", and "Non-CVD death" represent health states. "MI", "Stroke", "Hospitalization for unstable angina pectoris", and "Coronary revascularization" represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH EVOLOCUMAB																
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION								
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	982	15	6	8	26	11	7	7
2	0	0	0	0	0	0	0	0	964	20	6	11	35	22	14	14
3	0	0	0	0	0	0	0	0	944	22	7	12	38	35	21	21
4	0	0	0	0	0	0	0	0	922	24	7	13	42	49	30	30
5	0	0	0	0	0	0	0	0	898	26	8	14	45	64	38	38
6	0	0	0	0	0	0	0	0	872	29	8	15	50	80	48	48
7	0	0	0	0	0	0	0	0	843	31	8	17	54	99	58	58
8	0	0	0	0	0	0	0	0	813	34	9	18	59	119	69	69
9	0	0	0	0	0	0	0	0	780	37	9	20	64	140	80	80
10	0	0	0	0	0	0	0	0	744	40	10	21	69	164	92	92
11	0	0	0	0	0	0	0	0	706	43	10	23	74	189	105	105
12	0	0	0	0	0	0	0	0	665	43	11	23	74	217	118	118
13	0	0	0	0	0	0	0	0	622	44	11	23	76	246	132	132
14	0	0	0	0	0	0	0	0	576	44	11	23	76	278	146	146
15	0	0	0	0	0	0	0	0	528	44	11	23	76	311	161	161
16	0	0	0	0	0	0	0	0	478	43	11	23	74	346	175	175
17	0	0	0	0	0	0	0	0	427	42	11	22	72	382	190	190
18	0	0	0	0	0	0	0	0	376	40	11	21	69	420	205	205
19	0	0	0	0	0	0	0	0	324	37	10	20	65	457	219	219
20	0	0	0	0	0	0	0	0	273	34	10	18	59	494	232	232
21	0	0	0	0	0	0	0	0	224	31	9	16	53	531	245	245
22	0	0	0	0	0	0	0	0	178	27	8	14	46	565	257	257
23	0	0	0	0	0	0	0	0	136	22	7	12	39	597	267	267
24	0	0	0	0	0	0	0	0	100	18	6	10	31	625	276	276
25	0	0	0	0	0	0	0	0	69	14	4	7	24	649	283	283
26	0	0	0	0	0	0	0	0	44	10	3	5	17	668	288	288
27	0	0	0	0	0	0	0	0	26	7	2	4	12	682	292	292

WITHOUT EVOLOCUMAB																
Cycle	PRIMARY PREVENTION							SECONDARY PREVENTION								
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	983	21	6	8	33	11	7	7
2	0	0	0	0	0	0	0	0	965	29	7	11	46	22	13	13
3	0	0	0	0	0	0	0	0	945	31	7	12	50	35	21	21
4	0	0	0	0	0	0	0	0	923	34	8	13	55	49	28	28
5	0	0	0	0	0	0	0	0	899	38	8	15	61	64	37	37
6	0	0	0	0	0	0	0	0	873	42	9	16	67	81	46	46
7	0	0	0	0	0	0	0	0	845	45	9	18	73	99	55	55
8	0	0	0	0	0	0	0	0	815	50	10	19	80	120	66	66
9	0	0	0	0	0	0	0	0	782	54	10	21	87	142	77	77
10	0	0	0	0	0	0	0	0	746	59	11	23	94	166	88	88
11	0	0	0	0	0	0	0	0	707	57	11	22	92	192	100	100
12	0	0	0	0	0	0	0	0	666	58	11	23	94	221	113	113
13	0	0	0	0	0	0	0	0	622	59	12	23	95	251	126	126
14	0	0	0	0	0	0	0	0	576	59	12	23	96	284	140	140
15	0	0	0	0	0	0	0	0	527	59	12	23	95	319	154	154
16	0	0	0	0	0	0	0	0	477	58	12	22	93	355	168	168
17	0	0	0	0	0	0	0	0	425	56	12	22	90	393	182	182
18	0	0	0	0	0	0	0	0	372	53	11	21	85	432	196	196
19	0	0	0	0	0	0	0	0	319	49	11	19	79	471	210	210
20	0	0	0	0	0	0	0	0	268	45	10	17	72	510	222	222
21	0	0	0	0	0	0	0	0	218	40	9	15	64	548	234	234
22	0	0	0	0	0	0	0	0	172	34	8	13	55	583	245	245
23	0	0	0	0	0	0	0	0	130	29	7	11	46	615	255	255
24	0	0	0	0	0	0	0	0	94	23	5	9	36	644	262	262
25	0	0	0	0	0	0	0	0	64	17	4	7	28	668	269	269
26	0	0	0	0	0	0	0	0	40	12	3	5	20	686	274	274
27	0	0	0	0	0	0	0	0	23	8	2	3	13	700	277	277

Table 25: Markov Model secondary prevention cohort with and without evolocumab (under 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. “Alive without CVD”, “Alive with CVD”, “CVD death”, and “Non-CVD death” represent health states. “MI”, “Stroke”, “Hospitalization for unstable angina pectoris”, and “Coronary revascularization” represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH EVOLOCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	976	20	8	10	34	15	9	
2	0	0	0	0	0	0	0	0	951	28	8	15	48	31	18	
3	0	0	0	0	0	0	0	0	924	30	8	16	52	48	28	
4	0	0	0	0	0	0	0	0	894	33	9	17	57	67	39	
5	0	0	0	0	0	0	0	0	862	36	9	19	62	88	50	
6	0	0	0	0	0	0	0	0	827	39	10	20	67	111	62	
7	0	0	0	0	0	0	0	0	790	42	10	22	72	135	75	
8	0	0	0	0	0	0	0	0	750	45	11	24	78	162	88	
9	0	0	0	0	0	0	0	0	707	48	11	25	83	191	102	
10	0	0	0	0	0	0	0	0	662	46	12	24	80	222	116	
11	0	0	0	0	0	0	0	0	614	46	12	24	80	255	131	
12	0	0	0	0	0	0	0	0	564	46	12	24	80	290	147	
13	0	0	0	0	0	0	0	0	512	45	12	24	79	326	162	
14	0	0	0	0	0	0	0	0	458	44	12	23	77	364	178	
15	0	0	0	0	0	0	0	0	403	42	11	22	73	404	193	
16	0	0	0	0	0	0	0	0	349	40	11	21	69	443	208	
17	0	0	0	0	0	0	0	0	295	37	10	19	63	483	222	
18	0	0	0	0	0	0	0	0	243	33	9	17	57	521	236	
19	0	0	0	0	0	0	0	0	194	29	8	15	50	558	248	
20	0	0	0	0	0	0	0	0	149	24	7	13	42	592	259	
21	0	0	0	0	0	0	0	0	110	20	6	10	34	622	269	
22	0	0	0	0	0	0	0	0	76	15	5	8	26	648	276	
23	0	0	0	0	0	0	0	0	49	11	4	6	19	669	282	
24	0	0	0	0	0	0	0	0	29	8	3	4	13	684	287	
25	0	0	0	0	0	0	0	0	15	5	2	2	8	695	290	
26	0	0	0	0	0	0	0	0	7	3	1	1	4	702	291	
27	0	0	0	0	0	0	0	0	3	1	0	0	1	705	292	
WITHOUT EVOLOCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	975	27	9	11	44	16	9	
2	0	0	0	0	0	0	0	0	950	41	8	16	66	32	18	
3	0	0	0	0	0	0	0	0	923	44	9	17	70	50	27	
4	0	0	0	0	0	0	0	0	893	48	10	19	77	69	37	
5	0	0	0	0	0	0	0	0	861	52	10	20	84	91	48	
6	0	0	0	0	0	0	0	0	826	57	11	22	92	114	60	
7	0	0	0	0	0	0	0	0	788	62	11	24	99	140	72	
8	0	0	0	0	0	0	0	0	747	60	12	23	97	167	85	
9	0	0	0	0	0	0	0	0	704	62	12	24	99	198	98	
10	0	0	0	0	0	0	0	0	658	63	12	24	101	230	112	
11	0	0	0	0	0	0	0	0	609	63	12	24	101	265	127	
12	0	0	0	0	0	0	0	0	557	62	13	24	100	301	142	
13	0	0	0	0	0	0	0	0	504	61	12	24	98	340	157	
14	0	0	0	0	0	0	0	0	449	59	12	23	95	380	171	
15	0	0	0	0	0	0	0	0	393	56	12	22	90	421	186	
16	0	0	0	0	0	0	0	0	337	52	11	20	84	462	200	
17	0	0	0	0	0	0	0	0	283	48	10	18	76	503	214	
18	0	0	0	0	0	0	0	0	230	42	9	16	68	543	226	
19	0	0	0	0	0	0	0	0	182	36	8	14	58	580	238	
20	0	0	0	0	0	0	0	0	137	30	7	12	48	615	248	
21	0	0	0	0	0	0	0	0	99	24	6	9	39	645	256	
22	0	0	0	0	0	0	0	0	67	18	4	7	29	670	263	
23	0	0	0	0	0	0	0	0	42	13	3	5	21	690	268	
24	0	0	0	0	0	0	0	0	24	8	2	3	14	704	272	
25	0	0	0	0	0	0	0	0	14	4	1	2	6	712	274	
26	0	0	0	0	0	0	0	0	7	2	1	1	4	718	276	
27	0	0	0	0	0	0	0	0	3	1	0	0	2	721	276	

Table 26: Markov Model secondary prevention cohort with and without evolocumab (over 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. "Alive without CVD", "Alive with CVD", "CVD death", and "Non-CVD death" represent health states. "MI", "Stroke", "Hospitalization for unstable angina pectoris", and "Coronary revascularization" represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH ALIROCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	983	26	4	1	30	13	4	4
2	0	0	0	0	0	0	0	0	965	35	5	2	41	27	8	8
3	0	0	0	0	0	0	0	0	946	38	5	2	45	42	12	12
4	0	0	0	0	0	0	0	0	924	42	5	2	50	59	17	17
5	0	0	0	0	0	0	0	0	900	46	6	3	54	77	22	22
6	0	0	0	0	0	0	0	0	874	51	6	3	60	98	28	28
7	0	0	0	0	0	0	0	0	846	55	6	3	65	120	34	34
8	0	0	0	0	0	0	0	0	815	60	7	3	71	145	40	40
9	0	0	0	0	0	0	0	0	781	66	7	4	77	172	47	47
10	0	0	0	0	0	0	0	0	745	71	7	4	83	202	54	54
11	0	0	0	0	0	0	0	0	705	70	8	4	82	234	61	61
12	0	0	0	0	0	0	0	0	663	71	8	4	84	268	69	69
13	0	0	0	0	0	0	0	0	617	72	8	4	85	306	77	77
14	0	0	0	0	0	0	0	0	569	72	8	4	85	345	85	85
15	0	0	0	0	0	0	0	0	518	71	8	4	84	388	94	94
16	0	0	0	0	0	0	0	0	466	70	8	4	82	432	102	102
17	0	0	0	0	0	0	0	0	412	67	8	4	78	478	111	111
18	0	0	0	0	0	0	0	0	357	63	8	4	74	524	119	119
19	0	0	0	0	0	0	0	0	302	58	7	3	68	571	127	127
20	0	0	0	0	0	0	0	0	248	52	7	3	61	617	135	135
21	0	0	0	0	0	0	0	0	198	45	6	3	53	660	142	142
22	0	0	0	0	0	0	0	0	151	38	5	2	45	701	148	148
23	0	0	0	0	0	0	0	0	110	31	4	2	36	737	153	153
24	0	0	0	0	0	0	0	0	75	24	3	1	28	767	158	158
25	0	0	0	0	0	0	0	0	47	17	2	1	20	792	161	161
26	0	0	0	0	0	0	0	0	27	11	2	1	13	810	163	163
27	0	0	0	0	0	0	0	0	13	7	1	0	8	822	165	165

WITHOUT ALIROCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	981	28	6	2	33	15	5	5
2	0	0	0	0	0	0	0	0	960	40	6	3	46	30	10	10
3	0	0	0	0	0	0	0	0	938	43	6	3	50	47	15	15
4	0	0	0	0	0	0	0	0	914	47	7	4	55	65	21	21
5	0	0	0	0	0	0	0	0	887	52	7	4	60	85	27	27
6	0	0	0	0	0	0	0	0	858	57	8	5	65	108	34	34
7	0	0	0	0	0	0	0	0	826	62	8	5	71	133	41	41
8	0	0	0	0	0	0	0	0	792	67	8	5	77	160	49	49
9	0	0	0	0	0	0	0	0	754	72	9	6	83	189	57	57
10	0	0	0	0	0	0	0	0	714	71	9	6	82	221	65	65
11	0	0	0	0	0	0	0	0	670	73	9	6	84	256	74	74
12	0	0	0	0	0	0	0	0	624	73	10	6	85	293	83	83
13	0	0	0	0	0	0	0	0	575	73	10	6	85	333	93	93
14	0	0	0	0	0	0	0	0	523	73	10	6	84	374	102	102
15	0	0	0	0	0	0	0	0	470	71	10	6	82	418	112	112
16	0	0	0	0	0	0	0	0	415	68	9	5	78	464	122	122
17	0	0	0	0	0	0	0	0	359	64	9	5	74	510	131	131
18	0	0	0	0	0	0	0	0	303	59	9	5	68	556	140	140
19	0	0	0	0	0	0	0	0	250	53	8	4	61	602	149	149
20	0	0	0	0	0	0	0	0	198	46	7	4	53	645	156	156
21	0	0	0	0	0	0	0	0	152	39	6	3	45	685	163	163
22	0	0	0	0	0	0	0	0	110	31	5	2	36	721	169	169
23	0	0	0	0	0	0	0	0	75	24	4	2	28	751	174	174
24	0	0	0	0	0	0	0	0	47	17	3	1	20	775	178	178
25	0	0	0	0	0	0	0	0	27	11	2	1	13	793	181	181
26	0	0	0	0	0	0	0	0	13	7	1	1	8	805	182	182
27	0	0	0	0	0	0	0	0	6	3	1	0	3	811	183	183

Table 27: Markov Model secondary prevention cohort with and without alirocumab (under 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. “Alive without CVD”, “Alive with CVD”, “CVD death”, and “Non-CVD death” represent health states. “MI”, “Stroke”, “Hospitalization for unstable angina pectoris”, and “Coronary revascularization” represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

WITH ALIROCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	979	30	5	2	35	16	5	
2	0	0	0	0	0	0	0	0	958	43	5	2	50	33	10	
3	0	0	0	0	0	0	0	0	934	46	6	3	54	52	15	
4	0	0	0	0	0	0	0	0	908	51	6	3	60	72	20	
5	0	0	0	0	0	0	0	0	879	56	6	3	65	95	26	
6	0	0	0	0	0	0	0	0	848	61	7	3	71	119	33	
7	0	0	0	0	0	0	0	0	814	66	7	4	77	147	39	
8	0	0	0	0	0	0	0	0	777	71	7	4	84	176	47	
9	0	0	0	0	0	0	0	0	737	71	8	4	84	208	54	
10	0	0	0	0	0	0	0	0	694	73	8	4	86	243	62	
11	0	0	0	0	0	0	0	0	649	74	8	4	87	281	70	
12	0	0	0	0	0	0	0	0	600	74	8	4	87	321	79	
13	0	0	0	0	0	0	0	0	548	74	8	4	86	364	88	
14	0	0	0	0	0	0	0	0	494	72	8	4	85	409	96	
15	0	0	0	0	0	0	0	0	439	69	8	4	82	456	105	
16	0	0	0	0	0	0	0	0	383	66	8	4	77	504	114	
17	0	0	0	0	0	0	0	0	326	61	7	4	72	552	122	
18	0	0	0	0	0	0	0	0	271	55	7	3	65	599	130	
19	0	0	0	0	0	0	0	0	218	49	6	3	57	645	138	
20	0	0	0	0	0	0	0	0	168	41	5	2	49	688	144	
21	0	0	0	0	0	0	0	0	124	34	5	2	40	726	150	
22	0	0	0	0	0	0	0	0	86	26	4	2	31	759	155	
23	0	0	0	0	0	0	0	0	56	19	3	1	23	786	158	
24	0	0	0	0	0	0	0	0	32	13	2	1	15	807	161	
25	0	0	0	0	0	0	0	0	16	8	1	0	10	821	163	
26	0	0	0	0	0	0	0	0	7	4	1	0	5	829	164	
27	0	0	0	0	0	0	0	0	3	2	0	0	2	833	164	

WITHOUT ALIROCUMAB																
Cycle	PRIMARY PREVENTION								SECONDARY PREVENTION							
	Alive w/o CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death	Alive w/ CVD	MI	Stroke	Unstable AP	Coronary Revasc	CVD death	Non-CVD death		
0	0	0	0	0	0	0	0	0	1000	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	972	38	8	3	44	21	7	
2	0	0	0	0	0	0	0	0	944	56	8	5	65	43	13	
3	0	0	0	0	0	0	0	0	913	60	8	5	69	67	20	
4	0	0	0	0	0	0	0	0	879	66	9	5	76	93	28	
5	0	0	0	0	0	0	0	0	842	71	9	6	82	122	36	
6	0	0	0	0	0	0	0	0	802	77	9	6	89	153	45	
7	0	0	0	0	0	0	0	0	759	76	10	6	87	187	54	
8	0	0	0	0	0	0	0	0	713	77	10	6	89	224	63	
9	0	0	0	0	0	0	0	0	664	78	10	6	90	263	73	
10	0	0	0	0	0	0	0	0	612	78	10	6	90	306	83	
11	0	0	0	0	0	0	0	0	557	77	10	6	89	350	93	
12	0	0	0	0	0	0	0	0	500	75	10	6	87	397	103	
13	0	0	0	0	0	0	0	0	441	72	10	6	83	445	113	
14	0	0	0	0	0	0	0	0	382	68	10	5	78	495	123	
15	0	0	0	0	0	0	0	0	323	62	9	5	72	544	133	
16	0	0	0	0	0	0	0	0	266	56	8	4	65	592	142	
17	0	0	0	0	0	0	0	0	211	49	7	4	56	638	151	
18	0	0	0	0	0	0	0	0	161	41	6	3	47	681	158	
19	0	0	0	0	0	0	0	0	117	33	5	3	38	719	164	
20	0	0	0	0	0	0	0	0	80	25	4	2	29	751	169	
21	0	0	0	0	0	0	0	0	50	18	3	1	21	777	173	
22	0	0	0	0	0	0	0	0	28	12	2	1	14	796	176	
23	0	0	0	0	0	0	0	0	14	7	1	1	8	808	178	
24	0	0	0	0	0	0	0	0	7	3	1	0	4	815	179	
25	0	0	0	0	0	0	0	0	2	2	0	0	2	818	179	
26	0	0	0	0	0	0	0	0	1	1	0	0	1	820	180	
27	0	0	0	0	0	0	0	0	0	0	0	0	0	820	180	

Table 28: Markov Model secondary prevention cohort with and without alirocumab (over 65 years)

All values are presented as rounded to the nearest whole number; however, calculations were conducted with exact values. "Alive without CVD", "Alive with CVD", "CVD death", and "Non-CVD death" represent health states. "MI", "Stroke", "Hospitalization for unstable angina pectoris", and "Coronary revascularization" represent acute events that patients were at risk of experiencing between cycles leading to transitions across health states. The table presents the number of patients at the end of each cycle in one of the above-mentioned health states. Whereas acute events occur at any time during each cycle.

7 Curriculum Vitae

PERSONAL DETAILS

Name: Daniel Tobias Michaeli
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Place of birth: Bad Nauheim, Germany

EDUCATION

2023 – now National Center for Tumor Diseases (NCT) Heidelberg
Resident Physician in Internal Medicine (Oncology & Hematology)

2015 – 2022 Medical Faculty Mannheim, University of Heidelberg, Germany
Medicine: M1 (4th September, 2017), M2 (7th October, 2021), M3
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2007 – 2015 Weidigschule Butzbach, Germany
Abitur (12th June, 2015)

AWARDS

2024 Young Talent Award of the National Decade against Cancer from
the Federal Ministry of Education and Research

2023 Young Scientist Award from the German Cancer Society

2022 Science Award from the German Society for Market Access

2017 Scholarship from the German Academic Scholarship Foundation

2015 Physics Award (“Abiturpreis”) from the German Physical Society

8 Acknowledgements

At this point, I would like to thank everyone who directly or indirectly helped me in writing this dissertation.

I express my deepest gratitude to my supervisor Priv.-Doz. Dr. med. Tobias Boch for the opportunity to conduct this dissertation with him. I particularly thank him for the freedom to shape the scientific topics of this work according to my personal interests.

I am extremely grateful to my parents, Dr. med. Charlotte and Rainer Michaeli, and my siblings, Dr. med. Dr. rer. oec. Thomas, Dr. med. Julia and Stephan Michaeli, for their constant support in all my work. Without your loving support and encouragement throughout all phases of my life, I would have never made it this far.