Supplementary Online Content

Clinical Drug Investigation

Cost-Effectiveness of Icosapent Ethyl, Evolocumab, Alirocumab, Ezetimibe, or Fenofibrate in Combination with Statins Compared to Statin Monotherapy. DT Michaeli, JC Michaeli, T Boch, T Michaeli.

This supplementary material has been provided by the authors to give readers additional information about their work.

	Cholesterol-Lowering Strategy			**Triglyceride-Lowering Strategy**	
	Ezetimibe	Evolocuma	Alirocumab	Icosapent Ethyl	Fenofibrate
Name	IMPROVE-IT	FOURIER	ODYSSEY	REDUCE-IT	ACCORD
Reference	[1]	[2]	[3]	[4]	[5]
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 e1 Characteristics of cardiovascular outcome trials evaluating for lipid-modifying agents

CVOT cardiovascular outcome trial, *MACE* major adverse cardiovascular event, *NR* not reported.

	Icosapent Ethyl		Evolocumab		Alirocumab		Ezetimibe		Fenofibrate	
	Statin + Treatment	Statin	Statin + Treatment	Statin	Statin + Treatment	Statin	Statin + Treatment	Statin	Statin + Treatment	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 e2 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) [1–5]. Adopted from Michaeli et al. (2020) [6]. *CVD* cardiovascular disease, *MACE* major adverse cardiovascular event, *MI* myocardial infarct, *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.

Scenario	Primary Prevention		Secondary Prevention				
	Icosapent Ethyl	Fenofibrate	Icosapent Ethyl	Evolocumab	Alirocumab	Ezetimibe	Fenofibrate
Annual treatment cost							
Base case	19,485	-9,932	13,317	85,193	54,211	-4,231	-7,472
-50%	2,546	-11,383	792	33,303	21,616	-7,463	-8,376
+50%	36,424	-8,480	25,842	137,082	86,806	-998	-6,568
Discount rate							
3.5% (Base case)	19,485	-9,932	13,317	85,193	54,211	-4,231	-7,472
2.0%	16,141	-10,178	11,196	74,008	48,011	-4,702	-7,491
5.0%	23,330	-9,634	15,715	98,142	61,206	-3,673	-7,433
Yearly CVD risk increase							
+14% (Base Case)	19,485	-9,932	13,317	85,193	54,211	-4,231	-7,472
+12%	29,839	-7,386	18,423	117,177	68,895	-1,457	-5,951
+16%	12,290	-11,709	9,321	62,451	42,670	-6,358	-8,604
Yearly non-CVD risk increase							
+10% (Base Case)	19,485	-9,932	13,285	85,193	54,211	-4,231	-7,472
+8%	19,675	-11,382	13,233	89,681	55,573	-5,725	-8,713
+12%	19,186	-8,314	13,317	79,801	52,550	-2,694	-6,085

Table e3 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.

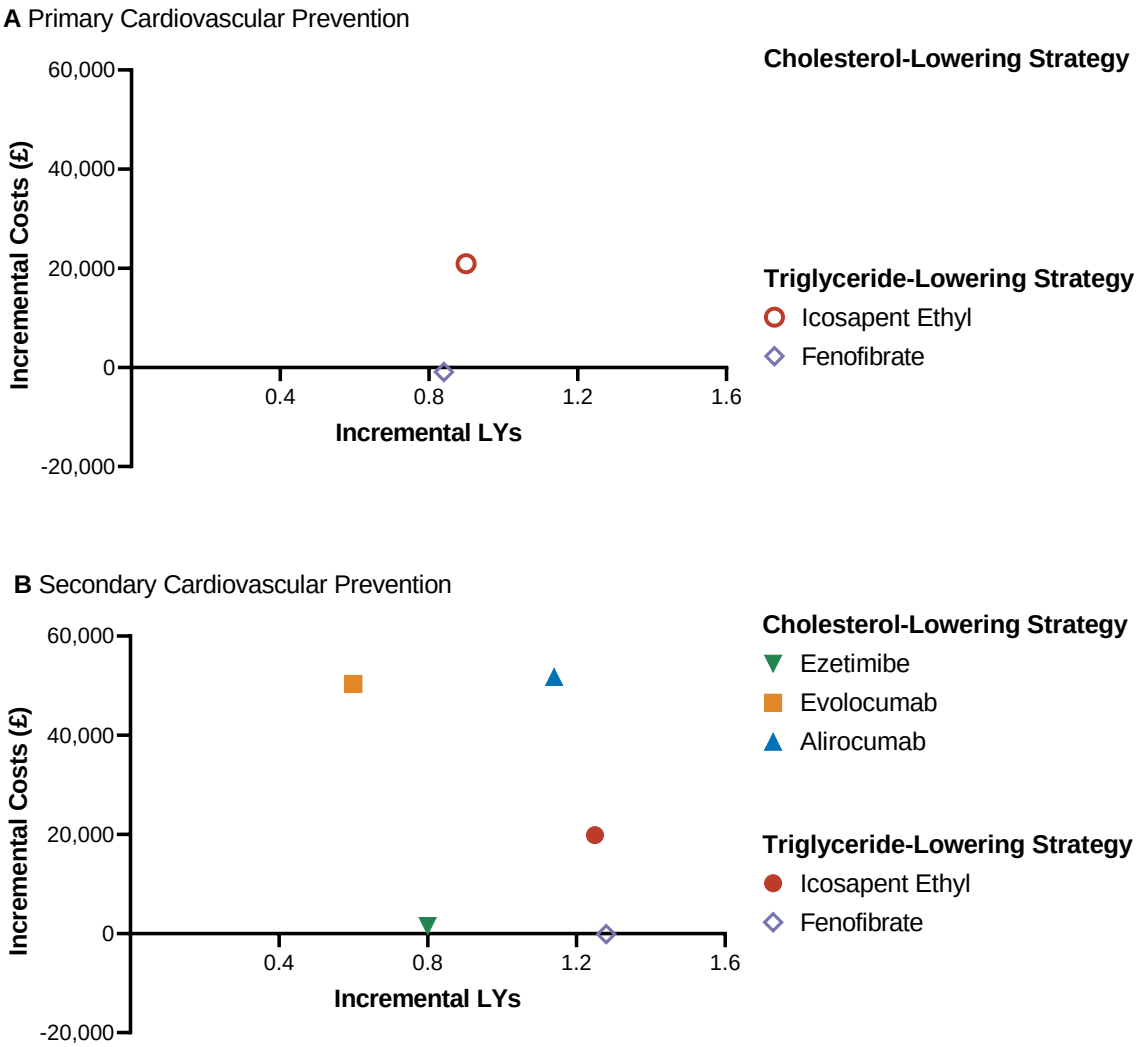

Figure e1 Cost-effectiveness plane for ezetimibe, evolocumab, alirocumab, icosapent ethyl, and fenofibrate in combination with statins for primary (**A**) and secondary (**B**) cardiovascular prevention by life years gained

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.[7] Costs in 2021 Great Britain Pounds (£). *LY* life year.

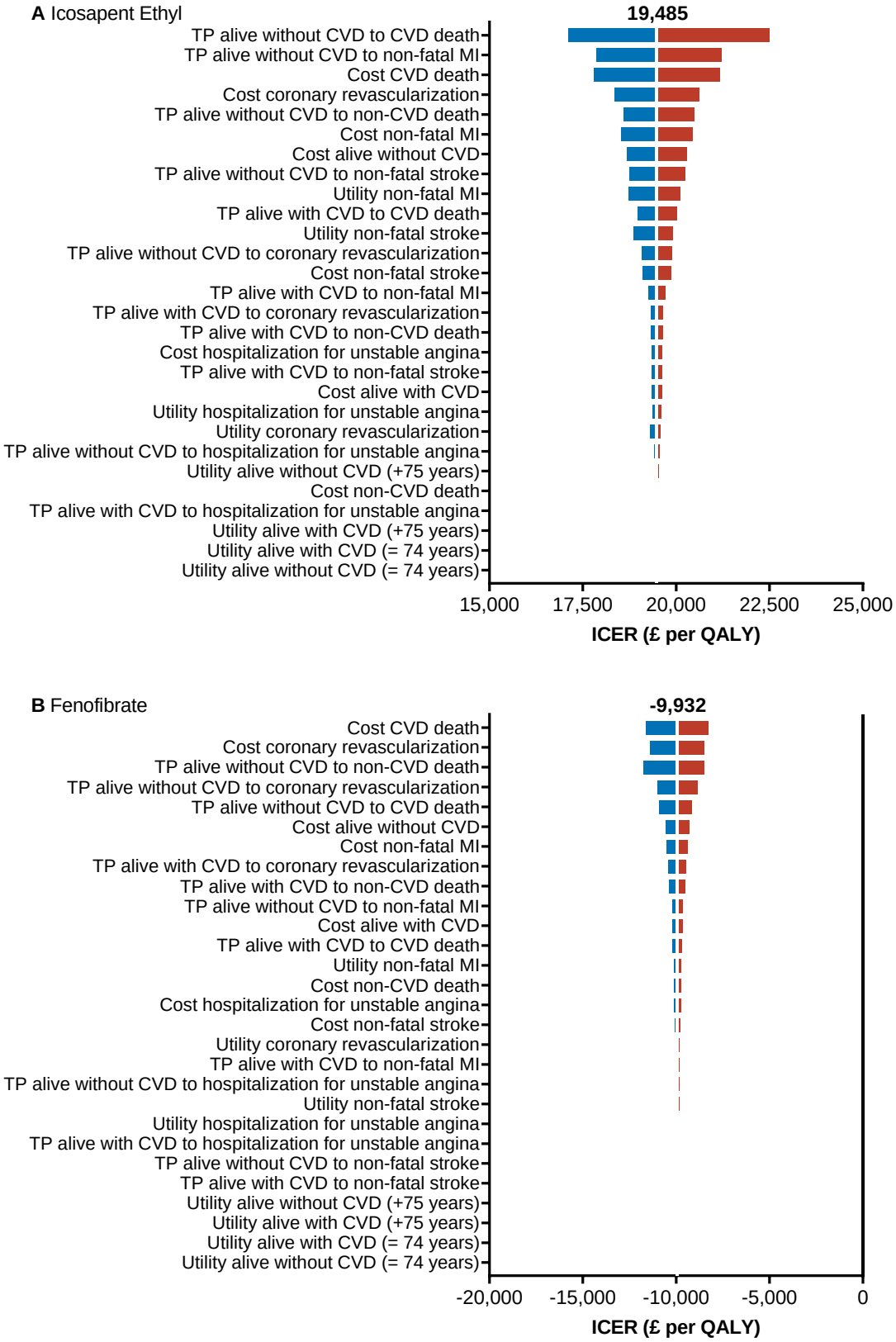

Figure e2 Univariate sensitivity analysis for primary cardiovascular prevention: tornado plots

Results displayed for icosapent ethyl (**A**) and fenofibrate (**B**). Graphs visualize the variation of input parameters by their confidence intervals presented in Table 1. Costs in 2021 Great Britain Pounds (£). *CVD* cardiovascular disease, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarct, *TP* transition probability.

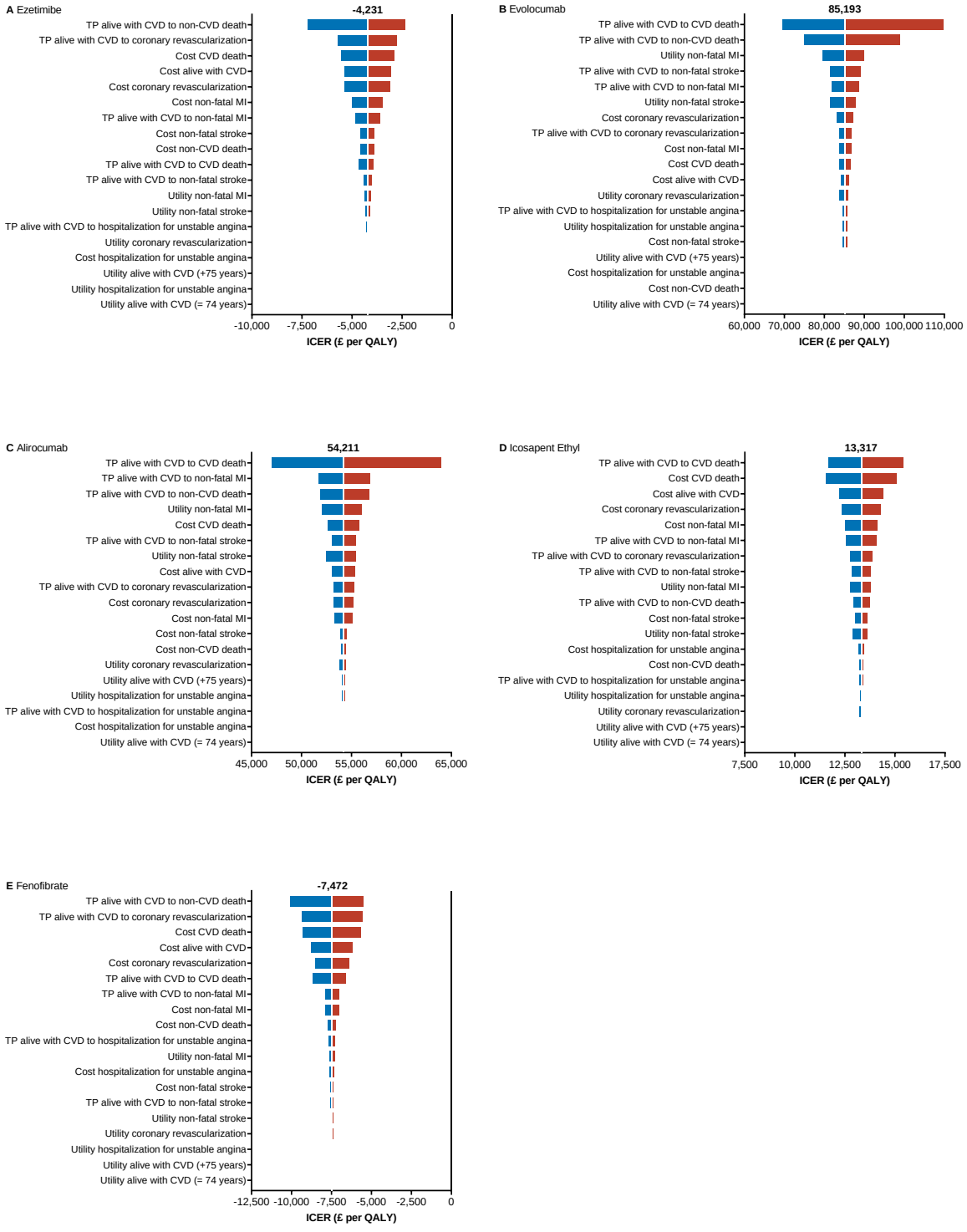

Figure e3 Univariate sensitivity analysis for secondary cardiovascular prevention: tornado plots

Results displayed for eztimibe (**A**), evolocumab (**B**), alirocumab (**C**), icosapent ethyl (**D**), and fenofibrate (**E**). Graphs visualize the variation of input parameters by their confidence intervals presented in Table 1. Costs in 2021 Great Britain Pounds (£). *CVD* cardiovascular disease, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarct, *TP* transition probability.

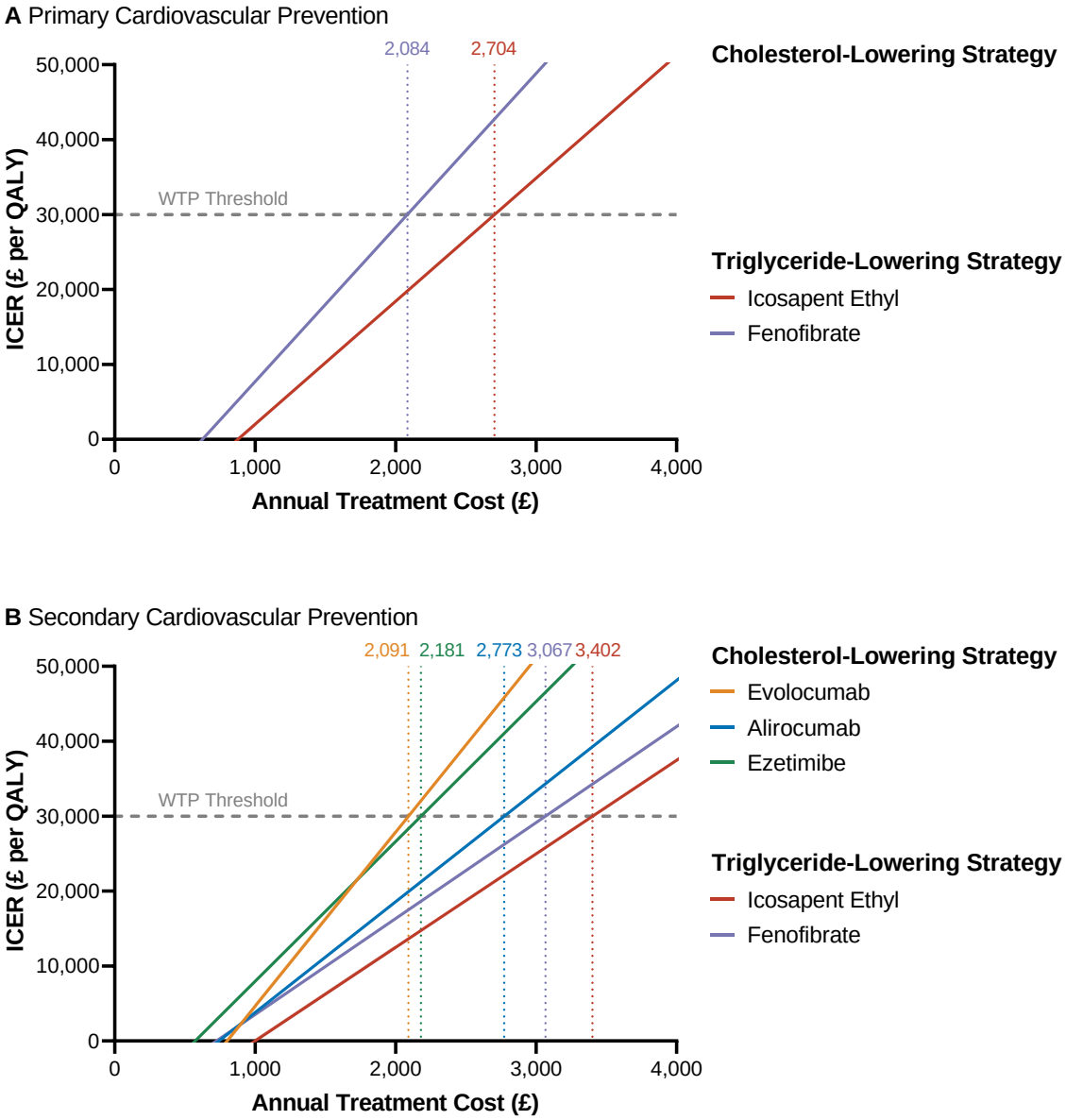

Figure e4 Incremental cost-effectiveness ratios as a function of the annual treatment cost at a willingness-to-pay threshold of £30,000 per QALY

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.[7] Costs in 2021 Great Britain Pounds (£). *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year.

References

1. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. Massachusetts Medical Society; 2015;372:2387–97.

2. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. Massachusetts Medical Society; 2017;376:1713–22.

3. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. Massachusetts Medical Society; 2018;379:2097–107.

4. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. Massachusetts Medical Society; 2019;380:11–22.

5. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.

6. Michaeli DT, Michaeli JC, Boch T, Michaeli T. Cost-Effectiveness of Lipid-Lowering Therapies for Cardiovascular Prevention in Germany. Cardiovasc Drugs Ther. 2022.

7. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41:111–88.