Supplementary Online Content

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

	Icosapent Ethyl		Evolocumab		Alirocumab		Ezetimibe		Fibrate	
	Treatment + Statin	Statin	Treatment + Statin	Statin	Treatment + Statin	Statin	Treatment + Statin	Statin	Treatment + 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 e1 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 fibrate (ACCORD) [1–5]. *MI* myocardial infarct, *CVD* cardiovascular disease.

Parameter	Fibrate		
	Value	Variation	Ref.
HAZARD RATIOS			
Alive without CVD (primary prevention)			
Non-fatal MI	0.98	(0.84,1.13)	[5]
CVD death	0.92	(0.78,1.06)	[5]
Non-CVD death	1.03	(0.87,1.18)	[5]
Non-fatal stroke	1.13	(0.96,1.29)	[5]
Hospitalization for unstable angina	1.05	(0.89,1.21)	[5]
Coronary revascularization	1.06	(0.90,1.21)	[5]
Alive with CVD (secondary prevention)			
Non-fatal MI	0.88	(0.75,1.01)	[5]
CVD death	0.82	(0.70,0.95)	[5]
Non-CVD death	0.92	(0.79,1.06)	[5]
Non-fatal stroke	1.01	(0.86,1.17)	[5]
Hospitalization for unstable angina	0.94	(0.80,1.08)	[5]
Coronary revascularization	0.94	(0.80,1.08)	[5]
UTILITIES			
Alive without CVD			
65-70 years	0.65	(0.64,0.67)	[6]
70+ years	0.63	(0.62,0.65)	[6]
Alive with CVD			
65-70 years	0.57	(0.56,0.59)	[7]
70+ years	0.55	(0.54,0.57)	[7]
Decrements			
Non-fatal MI	0.04	(0.02,0.05)	[8]
Non-fatal stroke	0.12	(0.09,0.16)	[8]
Hospitalization for unstable angina	0.09	(0.06,0.13)	[8]
Coronary revascularization	0.01	(0.01,0.03)	[8]
COSTS			
Alive without CVD	4,522	(±25%)	[9]
Alive with CVD	8,008	(±25%)	[10,11]
Non-fatal MI	8,588	(±25%)	[11]
CVD death	11,842	(±25%)	[10–13]
Non-CVD death	3,924	(±25%)	[12–14]
Non-fatal stroke	10,441	(±25%)	[11]
Hospitalization for unstable angina	4,791	(±25%)	[10]
Coronary revascularization	9,901	(±25%)	[10]
Annual treatment cost	130		[15]
Annual statin cost	132		[15]
OTHERS			
Discount rate	0.03	(0.00,0.10)	[16]
Annual CVD risk increase	0.14	(±25%)	[17]
Annual non-CVD risk increase	0.10	(±25%)	[17]

Table e2 Model input parameters: base case value, variation, and distribution for hazard ratios, utilities, and costs (fibrate)

The table displays each drug's key input parameters used for the base case scenario of the cost-effectiveness model. Variation columns display upper and lower bound of parameter values that were used for sensitivity analysis. For hazard ratios and utilities, this variation equates to 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 Supplement Table e1. *CVD* cardiovascular disease, *MI* myocardial infarct, *NA* not applicable.

Scenario	Primary Prevention		Secondary Prevention				
	Icosapent Ethyl	Fibrate	Icosapent Ethyl	Evolocumab	Alirocumab	Ezetimibe	Fibrate
Annual Treatment Cost							
Base Case	18,133	-16,632	14,485	114,639	100,532	-5,584	-10,305
-50%	-1,815	-18,000	-875	45,752	43,561	-9,059	-11,171
+50%	38,081	-15,264	29,845	183,525	157,503	-2,108	-9,440
Discount rate							
3% (Base Case)	18,133	-16,632	14,485	114,639	100,532	-5,584	-10,305
0%	10,973	-16,986	9,642	87,203	80,034	-6,456	-10,208
10%	45,014	-14,925	31,472	219,622	172,130	-1,940	-10,234
Yearly CVD risk increase							
+14% (Base Case)	18,133	-16,632	14,485	114,639	100,532	-5,584	-10,305
+10.5%	43,087	-9,516	27,470	200,370	149,672	1,796	-5,955
+17.5%	5,211	-20,269	6,405	67,249	68,229	-10,261	-12,935
Yearly non-CVD risk increase							
+10% (Base Case)	18,133	-16,632	14,485	114,639	100,532	-5,584	-10,305
+7.5%	18,001	-19,646	14,099	121,163	103,476	-8,810	-12,878
+12.5%	18,215	-13,149	14,947	106,353	96,752	-2,187	-7,319
Early lipid lowering treatment							
Start at 55 for 25 years	9,381	-13,070	9,822	71,899	70,379	-6,348	-7,194

Table e3 Scenario analysis for the incremental cost-effectiveness ratio (ICER 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.

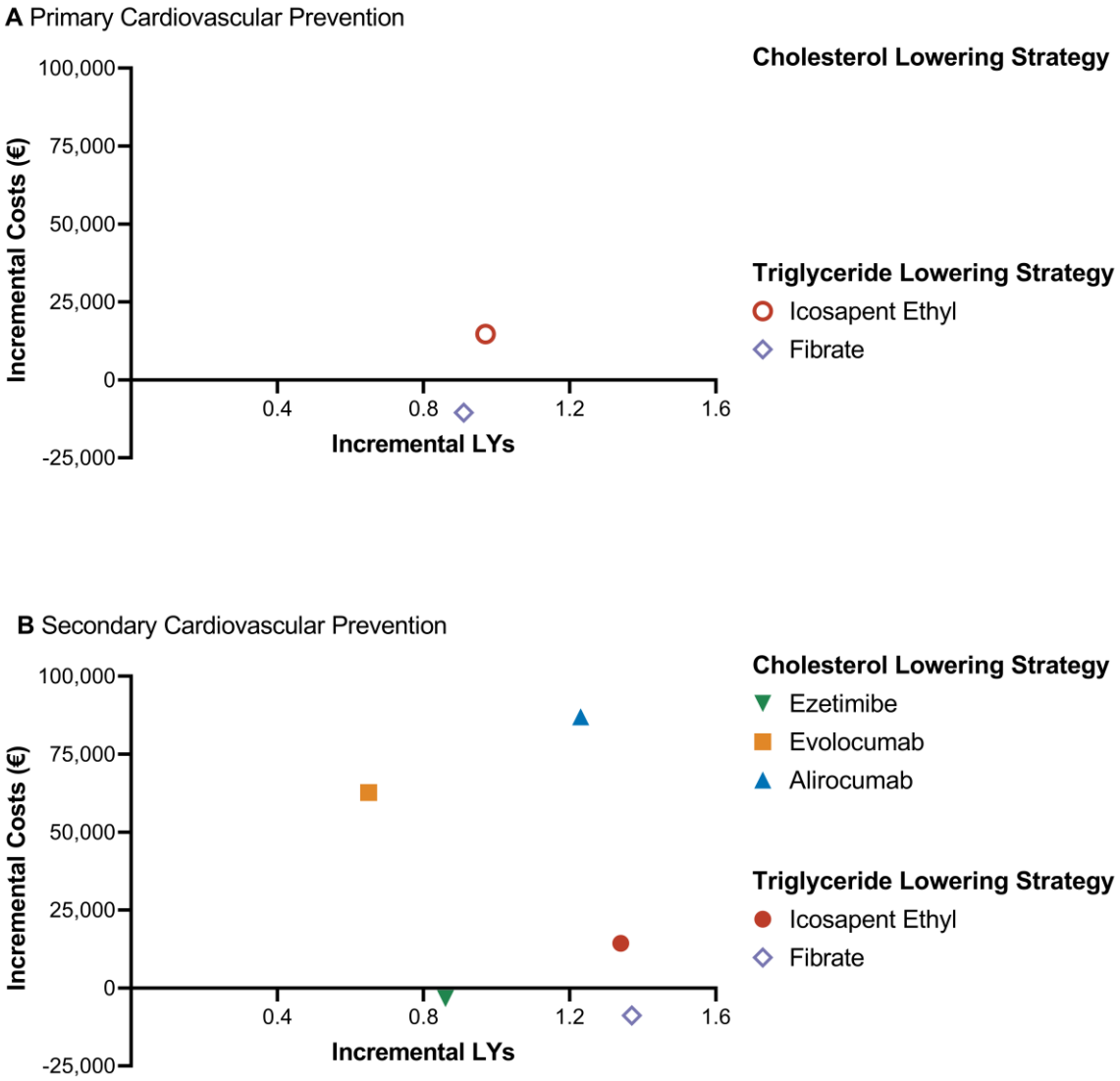

Figure e1 Cost-effectiveness plane with efficiency frontier for cholesterol and triglyceride lowering treatment strategies in combination with statin by life years gained

Resulats 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 in cholesterol lowering (ezetimibe, alirocumab, evolocumab) and triglyceride lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines [18]. *LY* life year.

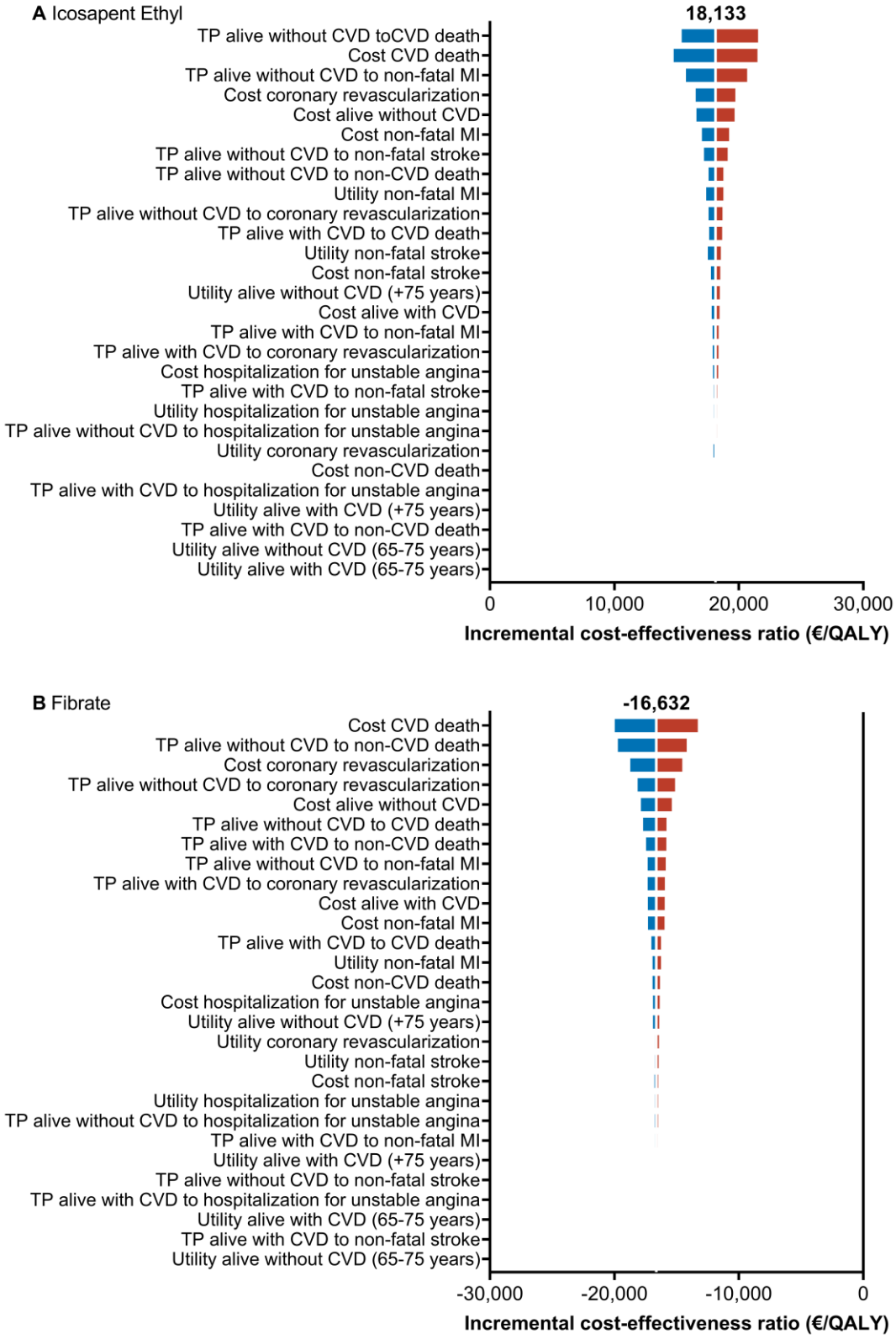

Figure e2 Tornado plots for primary cardiovascular prevention

Results are visualized for icosapent ethyl (**A**) and fibrate (**B**). Input parameters were varied by 95% confidence intervals displayed in Table 1. All costs are presented in Euros (€) and were inflation adjusted to 2021 values. *CVD* cardiovascular disease, *MI* myocardial infarct, *TP* transition probability.

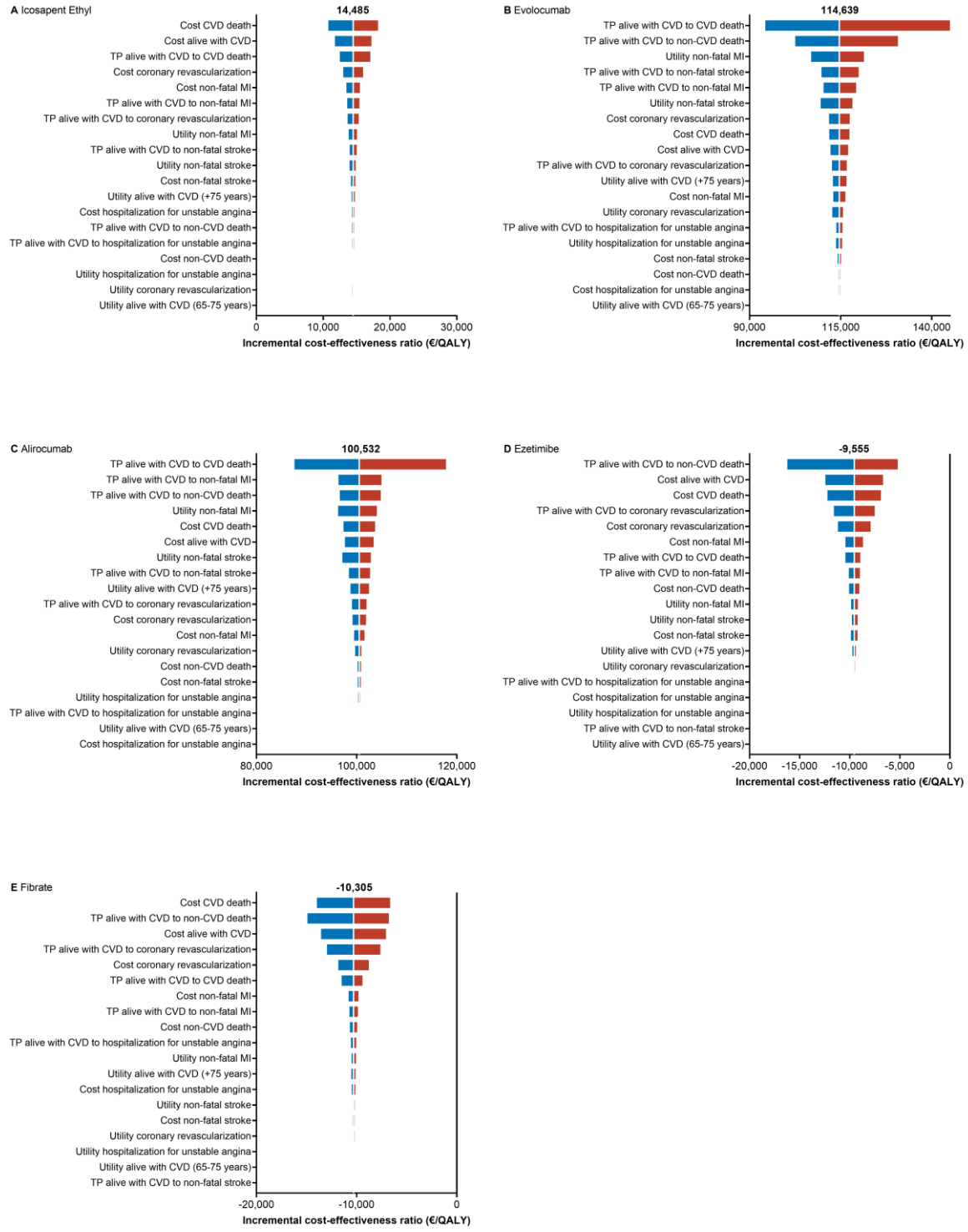

Figure e3 Tornado plots for secondary cardiovascular prevention

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 1. All costs are presented in Euros (€) and were inflation adjusted to 2021 values. *CVD* cardiovascular disease, *MI* myocardial infarct, *TP* transition probability.

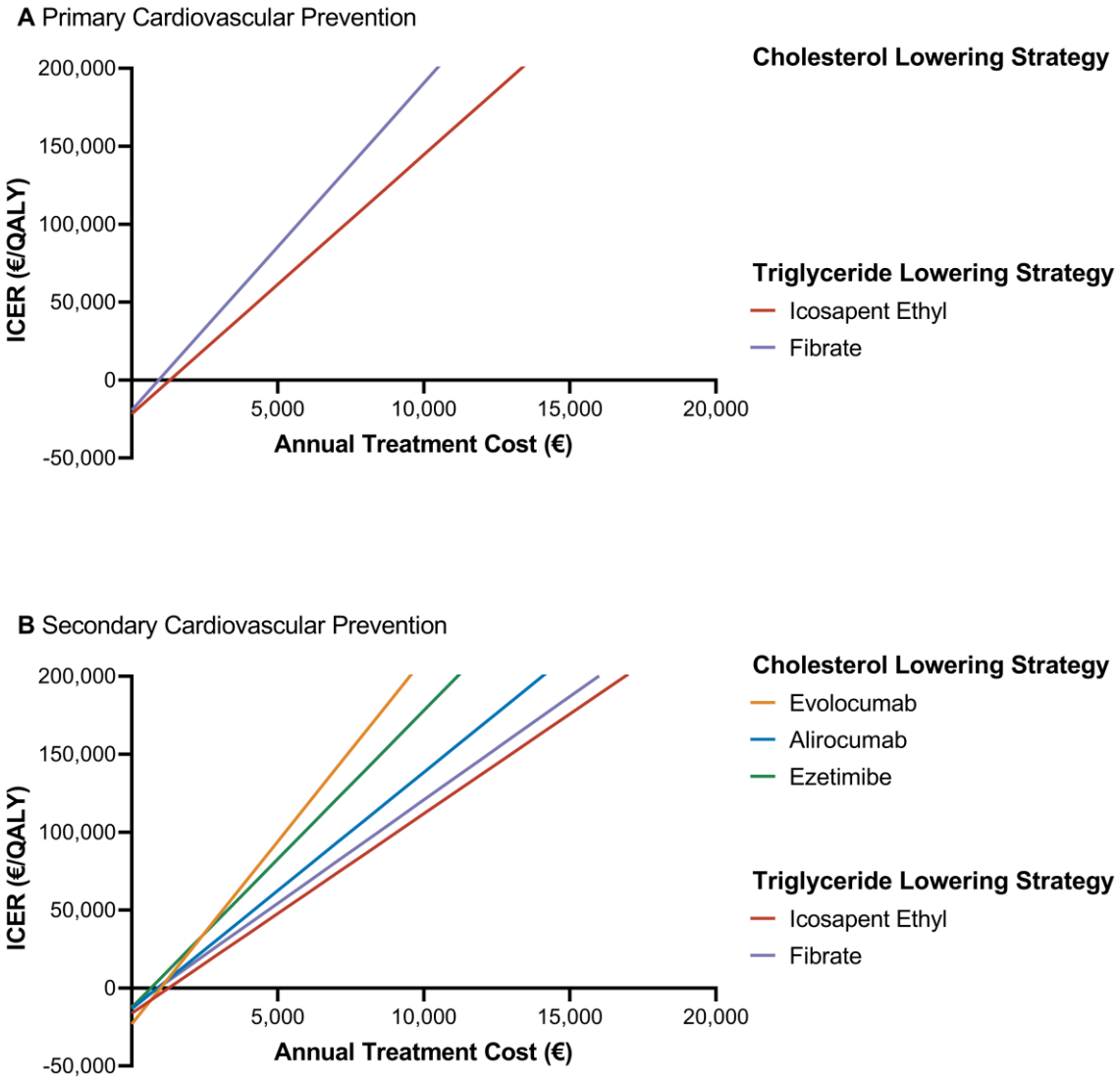

Figure e4 Incremental cost-effectiveness ratios as a function of the annual treatment cost

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 in cholesterol lowering (ezetimibe, alirocumab, evolocumab) and triglyceride lowering (icosapent ethyl, fibrate) strategies based on the European Society of Cardiology guidelines [18]. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year.

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