Eligibility Criteria PCSK9-I Target Trial

For the target trial, we have considered eligible subjects for the use of the monoclonal antibodies PCSK9-i in Italy.

1. **FAST TRACK**: subjects aged ≤ 80 years with recent acute myocardial infarction (AMI) (last 12 months) or multiple cardiovascular (ASCVD) events and a single measurement of LDL ≥ 70 mg/dl.
2. **SECONDARY PREVENTION:** subjects aged ≤ 80 years with either:
    - past atherosclerotic cardiovascular event (ASCVD): coronary artery bypass graft, stroke/TIA, angioplasty, coronary revascularization, carotid revascularization, peripheral arterial disease, diagnosis of ischemic heart disease
    - diabetes mellitus with target organ damage (TOD) i.e. microalbuminuria, retinopathy, neuropathy or renal insufficiency
    - diabetes with at least one risk factor among obesity, smoking, hypertension

    three consecutive determinations performed at different times (at least 2 months apart) ≥ 70 mg/dl and at least 6 months with high efficacy statin plus ezetimibe or with demonstrated intolerance.
3. **HETEROZYGOUS FAMILIAR HYPERCHOLESTEROLEMIA:** aged ≤ 80 years with Heterozygous Familiar Hypercholesterolemia and three consecutive determinations performed at different times (at least 2 months apart) ≥ 130 mg/dl and at least 6 months with high efficacy statin plus ezetimibe or with demonstrated intolerance.
4. **HOMOZYGOUS FAMILIAR HYPERCHOLESTEROLEMIA:** aged ≤ 80 years with Homozygous Familiar Hypercholesterolemia.

Definition of eligibility subgroups

The study population was divided in the mutually exclusive subgroups defined as follows from the key eligibility criteria:

- Subjects with a least one past atherosclerotic cardiovascular event (“ASCVD”)
- Diabetes with TOD or at least a Risk Factor (RF) among obesity, smoking, hypertension and no ASCVD (“Diabetes TOD/RF”)
- Diabetes with TOD or at least a Risk Factor (RF) and ASCVD (“Diabetes TOD/RF+ ASCVD”)

- Familiar Hypercholesterolemia (FH) without Diabetes TOD/RF or ASCVD

CHEERS Checklist

Section/topic	Item No	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title, Page 1 The study is identified as an individual-level decision health economic model involving PCSK9-I
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract, Page 2. The abstract is structured and includes objective, design, setting, outcome measures, results and conclusions
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction, page 4.
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	n.a.
Study population	5	Describe characteristics of the study population	Methods, Table 1 and Supplementary Material in which detail eligibility criteria for the study are described. Results, paragraph Study cohort
Setting and Location	6	Provide relevant contextual information that may influence findings.	Methods, Table 1 and paragraph “Data sources”
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Introduction, page 4 (last sentence) and Table 1.

Perspective	8	State the perspective(s) adopted by the study and why chosen.	Introduction, page 4 (last sentence)
Time horizon	9	State the time horizon for the study and why appropriate.	Methods, page 6 and Discussion, page 15.
Discount rate	10	Report the discount rate(s) and reason chosen	Methods, page 11.
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods, page 7 and 11
Measurements of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods, from page 9 to 11
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods, from page 6 to 11
Valuation of costs	14	Describe how costs were valued.	Methods, from page 6 to 11 and Supplementary Material from page 5 to page 9
Currency, price date and, conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods, Table 1 and page 11. Results, page 13
Rationale and description of the model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Introduction, page 4 and Methods, from page 8 to page 11
Analytics and Assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation	Models' assumption: Methods, from page 8 to page 12. Sensitivity analyses: Methods, page 12-13

		methods, and approaches for validating any model used.	
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods, page 7 and page 210
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	n.a.
Characterizing uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods, page 12-13
Approach engagement	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	n.a
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references), including uncertainty or distributional assumptions.	Supplementary Table 1, 2, 5, 6
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results, paragraph "Cost-effectiveness results", page 14 and 15, Table 3, Figure 3
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or	Results, paragraph "Cost-effectiveness results", page 14 and 15 and all the mentioned Figures

		projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	and Tables. Results, paragraph “Sensitivity analyses” and all the Figures mentioned.
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	n.a.
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion, from page 15 to page 17
Other relevant information			
Funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 2
Conflict of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Page 2

Definition of the hospitalization costs

The hospitalization cost model has both deterministic and stochastic components. The first stochastic component is the type of hospitalization (in-hospital state), the probability of which is determined over time by the disease multistate model. The cost associated with an individual's entry into a particular hospital state is also determined the DRG code. The DRG code is itself a random variable with a multinomial distribution with three parameters: the number of trials, which is set to 1; the number of possible events; a vector of probabilities. Both the number of possible events and the vector of probabilities depend on the specific in-hospital state entered. The number of possible events corresponds to the number of possible DRG codes for the state entered and the probabilities correspond to the probability of being assigned a particular DRG code for that in-hospital state. For each possible value of the DRG code, three deterministic quantities are determined: the fixed cost of the hospitalization, a threshold for the length of stay, and a time-varying daily cost that is activated if the hospitalization is longer than the threshold for the length of stay. Thus, the final cost of the hospitalization is determined by these quantities together with the length of stay, which is defined according to the disease multistate model. For each in-hospital state, the probability of each DRG code were estimated from the data as the proportion of hospitalization with a specific DRG code within each in-hospital state. All the quantities involved in the cost model are reported in Supplementary Table 1.**Supplementary Table 1** List of DRG codes, with corresponding probabilities and, price list used to define the cost-model.

State	DRG	Description	*Probability*	Cost *length of stay below threshold* (Euros)	Threshold (Days)	Cost *length of stay over threshold* (Euros/per-day)
ACS	557	Interventions on the cardiovascular system percutaneously with drug-eluting stent with major cardiovascular diagnosis	0.28	11723	15	434
ACS	124	Cardiovascular diseases excluding acute myocardial infarction, with cardiac catheterization and complicated diagnosis	0.176	5037	37	502
ACS	558	Interventions on the cardiovascular system percutaneously with drug-eluting stent without major cardiovascular diagnosis	0.203	10097	7	374
ACS	122	Cardiovascular diseases with acute myocardial infarction without major complications, discharged alive	0.108	5410	26	325
ACS	121	Cardiovascular diseases with acute myocardial infarction and major complications, discharged alive	0.122	6794	32	333
ACS	548	Coronary bypass with cardiac catheterization without major cardiovascular diagnosis	0.054	21698	52	911
ACS	550	Coronary bypass without cardiac catheterization without major cardiovascular diagnosis	0.027	17958	29	395
ACS	555	Interventions on the cardiovascular system percutaneously with major cardiovascular diagnosis	0.027	11723	15	434
IS	534	Extra cranial vascular interventions without major complications	0.444	6587	31	365

IS	559	Acute ischemic stroke with use of thrombolytic agents	0.296	5462	52	272
IS	524	Transient cerebral ischemia	0.185	3422	24	275
IS	16	Nonspecific cerebrovascular diseases with major complications	0.037	5474	41	288
IS	533	Extra cranial vascular interventions with major complications	0.037	6587	31	365
PAD	479	Other interventions on the cardiovascular system without major complications	0.480	5410	45	280
PAD	130	Peripheral vascular diseases with major complications	0.140	4904	48	296
PAD	110	Major interventions on the cardiovascular system with major complications	0.120	14177	61	392
PAD	131	Peripheral vascular diseases without major complications	0.120	3398	39	275
PAD	554	Other vascular interventions with major complications without major cardiovascular diagnosis	0.10	8223	62	316
PAD	113	Amputation for circulatory disorders excluding upper limb and toe amputations	0.04	13145	87	297
Others: CV	127	Heart failure and shock	0.259	4300	34	276
Others: CV	125	Cardiovascular diseases excluding acute myocardial infarction, with cardiac catheterization and uncomplicated diagnosis	0.089	2416	14	344
Others: CV	139	Arrhythmia and cardiac conduction abnormalities without major complications	0.067	2636	25	291
Others: CV	551	Implantation of permanent cardiac pacemaker with major cardiovascular diagnosis or automatic implantable cardioverter-defibrillator (AICD) or pulse generator	0.067	14717	41	604
Others: CV	140	Angina pectoris	0.044	3032	24	293
Others: CV	515	Implantation of cardiac defibrillator without cardiac catheterization	0.030	23705	30	474
Others: CV	104	Cardiac valve interventions and other major cardiothoracic procedures with cardiac catheterization	0.067	25492	48	943
Others: CV	111	Major interventions on the cardiovascular system without major complications	0.067	8693	45	322
Others: CV	144	Other circulatory system diagnoses with major complications	0.059	5487	37	328
Others: CV	518	Interventions on the cardiovascular system percutaneously without	0.052	7589	7	280

		coronary artery stent insertion without acute myocardial infarction				
Others: CV	105	Cardiac valve interventions and other major cardiothoracic procedures without cardiac catheterization	0.037	21551	38	433
Others: CV	129	Cardiac arrest of unknown cause	0.022	5620	56	279
Others: CV	142	Syncope and collapse without major complications	0.022	2509	21	199
Others: CV	547	Coronary bypass with cardiac catheterization with major cardiovascular diagnosis	0.037	21698	52	911
Others: CV	138	Arrhythmia and cardiac conduction abnormalities with major complications	0.030	4496	31	386
Others: CV	141	Syncope and collapse with major complications	0.022	3362	27	218
Others: CV	535	Implantation of cardiac defibrillator with cardiac catheterization with acute myocardial infarction, heart failure, or shock	0.022	28040	23	1037
Others: CV	103	Heart transplant or implantation of cardiac assist device	0.007	69501	70	804
Others: No CV	87	Pulmonary edema and respiratory failure	0.258	4400	31	297
Others: No CV	14	Intracranial hemorrhage or cerebral infarction	0.143	5462	52	272
Others: No CV	79	Respiratory infections and inflammations, age > 17 with major complications	0.134	9283	79	280
Others: No CV	576	Septicemia without mechanical ventilation ≥ 96 hours, age > 17	0.129	6974	51	293
Others: No CV	89	Simple pneumonia and pleurisy, age > 17 with major complications	0.106	5521	38	293
Others: No CV	566	Respiratory system diagnoses with assisted ventilation < 96 hours	0.051	13140	64	470
Others: No CV	565	Respiratory system diagnoses with assisted ventilation ≥ 96 hours	0.051	13140	64	470
Others: No CV	90	Simple pneumonia and pleurisy, age > 17 without major complications	0.041	3684	31	174
Others: No CV	78	Pulmonary embolism	0.032	5976	55	284
Others: No CV	80	Respiratory infections and inflammations, age > 17 without major complications	0.028	6769	92	259
Others: No CV	542	Tracheostomy with mechanical ventilation ≥ 96 hours or non-face, mouth, and neck-related primary diagnosis without major surgery	0.028	56885	132	680

Supplementary Table 2 Utilities used in Sensitivity Analysis D.

	PSA Distribution	Parameters
Before first hospitalization	Fixed	1
During an hospitalization[1]		
ASC	Gaussian	0.693 (0.004)
IS		0.649 (0.007)
PAD		0.701 (0.009)
OTHERS CV		0.6785 (0.0045)
OTHERS NON-CV		0.786 (0.001)
After first hospitalization	Gaussian	0.649 (0.007)
Death	Fixed	0

1. Morey JR, Jiang S, Klein S, et al. Estimating Long-Term Health Utility Scores and Expenditures for Cardiovascular Disease From the Medical Expenditure Panel Survey. *Circ Cardiovasc Qual Outcomes*. 2021;14(4):E006769. doi:10.1161/CIRCOUTCOMES.120.006769

Supplementary Table 3 *Descriptive statistics of study cohort*

	LLT N = 1,815	LLT+PCSK9-I N = 161	p-value*
Main characteristics at study entry			
Age, mean (SD)	68 (9)	65 (10)	<0.001
Gender			0.021
F	848 (47%)	60 (37%)	
M	967 (53%)	101 (63%)	
BMI	27.0 (25.0, 31.0)	27.0 (25.0, 30.0)	0.086
Charlson index	2.00 (1.00, 4.00)	2.00 (1.00, 4.00)	0.2
Stroke	175 (9.6%)	10 (6.2%)	0.2
COPD	410 (23%)	22 (14%)	0.009
Renal Disease	376 (21%)	23 (14%)	0.051
Obesity	354 (20%)	20 (12%)	0.028
Smoke	245 (13%)	27 (17%)	0.2
Hypertension	1,632 (90%)	137 (85%)	0.055
Eligibility subgroups			
Only ASCVD	442 (24%)	36 (22%)	<0.001
Diabetes TOD/RF (No ASCVD)	865 (48%)	12 (7.5%)	
Diabetes TOD/RF + ASCVD	450 (25%)	88 (55%)	
FH (No ASCVD, No Diabetes TOD, No RF)	58 (3%)	25 (16%)	
CV history			
Fast Track	744 (41%)	105 (65%)	<0.001
Previous NSTEMI	193 (11%)	31 (19%)	<0.001
Previous STEMI	243 (13%)	47 (29%)	<0.001
PTCA	357 (20%)	76 (47%)	<0.001
CABG	151 (8.3%)	33 (20%)	<0.001
PAD	238 (13%)	32 (20%)	0.017

Very High CV Risk	1,431 (79%)	130 (81%)	0.6
LDL (mg/dl), median (IQR)	114 (88, 148)	136 (107, 173)	<0.001
Previous history of LLT			
PDC	8% (2%-22%)	12% (4%-30%)	0.007
Time on LLT (years)	9.7 (4.6-15)	13 (7 – 19)	<0.001

*p-values were calculated using the t-test or the non-parametric Mann-Whitney test, Chi-squared or Fisher Exact test as appropriate.

ASCVD=Atherosclerotic cardiovascular disease; BMI=Body Mass Index; CABG=Coronary Artery Bypass Grafting; COPD= Chronic Obstructive Pulmonary Disease; CV=Cardio Vascular; FH=Familiar Hypercholesterolemia; LDL= Low-Density Lipoprotein ; LLT=Lipid-Lowering Therapy; TOD= Target Organ Damage; RF=Risk factor; PAD=Periphery Arterial Disease; PCSK9-I= Proprotein Convertase Subtilisin–Kexin type 9- Inibitor; PDC=Proportion of Days Covered; PTCA= Percutaneous Transluminal Coronary Angioplasty.

Supplementary Table 4 Propensity score diagnostics

Variable	Standardized effect size Unweighted Dataset	p-value for unbalance Unweighted Dataset	Standardized effect size Weighted Dataset	p-value for unbalance Weighted Dataset
Age	-0.136	0.159	0.076	0.554
Sex	0.129	0.153	-0.058	0.718
CHARLSON index	-0.003	0.973	-0.040	0.770
ASCVD	0.324	<0.001	-0.219	0.195
Diabetes with organ damage or risk factor	0.000	0.997	0.153	0.202
Time on statins	0.067	0.449	-0.028	0.773
PDC statins	0.065	0.477	-0.132	0.280
ACS multiple CV	0.259	0.003	-0.199	0.171
ACS NSTEMI	0.176	0.092	-0.040	0.681
ACS STEMI	0.381	<0.001	-0.030	0.750
Year of enrolment	-0.066	0.471	-0.127	0.467

ASCVD=Atherosclerotic cardiovascular disease; BMI=Body Mass Index; CABG=Coronary Artery Bypass Grafting; COPD= Chronic Obstructive Pulmonary Disease; CV=Cardio Vascular; FH=Familiar Hypercholesterolemia; LDL= Low-Density Lipoprotein ; LLT=Lipid-Lowering Therapy; TOD= Target Organ Damage; RF=Risk factor; PAD=Periphery Arterial Disease; PCSK9-I= Proprotein Convertase Subtilisin–Kexin type 9- Inhibitor; PDC=Proportion of Days Covered; PTCA= Percutaneous Transluminal Coronary Angioplasty.

Supplementary Table 5. Estimated parameters of all the transition hazards for the disease model. The parameters are all adjusted for age, sex, Charlson index, past atherosclerotic cardiovascular disease (ASCVD), diabetes with Target Organ Damage (TOD) or risk factor, the history of treatment with statins (duration and adherence) and the month/year eligibility date through IPTW.

Transition	**Parameter**	**Estimate**	95% **CI**
Toward death	gamma 0 Out-of-hospital death	-1.42	-3.42 ; 0.58
	gamma 1 Out-of-hospital death	1.18	0.59 ; 1.78
	gamma 2 Out-of-hospital death	0.06	0.02 ; 0.1
	gamma 3 Out-of-hospital death	-0.07	-0.12 ; -0.03
	gamma 1 IN-hospital vs. Out-of-hospital death	0.09	-0.55 ; 0.72
	gamma 2 IN-hospital vs. Out-of-hospital death	0.01	-0.01 ; 0.03
	gamma 0 2+ hospitalization vs. 1	0.57	0.09 ; 1.04
	gamma 0 IN-hospital vs. Out-of-hospital death	2.51	0.47 ; 4.55
	gamma0 PCSK9-i (Yes vs. No)	-1.99	-2.68 ; -1.3
Towards hospital	gamma 0 ACS	-4.67	-5.06 ; -4.29
	gamma 1 ACS	0.33	0.22 ; 0.44
	gamma 2 ACS	-0.01	-0.01 ; -0.01
	gamma 1 IS vs. ACS	0.19	-0.02 ; 0.41
	gamma 1 OTHERS CV vs. ACS	0.01	-0.1 ; 0.13

	gamma 1 OTHERS NO CV vs. ACS	0.10	-0.02 ; 0.21
	gamma 1 PAD vs. ACS	0.17	-0.03 ; 0.37
	gamma 0 2+ hospitalization vs. 1	3.41	3.18 ; 3.64
	gamma 0 IS vs. ACS	-1.01	-1.41 ; -0.62
	gamma 0 OTHERS CV vs. ACS	0.36	0.11 ; 0.62
	gamma 0 OTHERS NO CV vs. ACS	0.29	0.03 ; 0.54
	gamma 0 PAD vs. ACS	-0.91	-1.28 ; -0.54
	gamma0 PCSK9-i 1 (Yes vs. No)	-0.24	-0.46 ; -0.01
	gamma0 PCSK9-i 2+ (Yes vs. No)	-0.09	-0.47 ; 0.29
Towards out-of-hospital	gamma 0 ACS	8.06	6.84 ; 9.27
	gamma 1 ACS	1.77	1.51 ; 2.03
	gamma 2 ACS	0.05	0.03 ; 0.06
	gamma 1 IS vs. ACS	0.45	0.06 ; 0.84
	gamma 1 OTHERS CV vs. ACS	-0.04	-0.26 ; 0.19
	gamma 1 OTHERS NO CV vs. ACS	0.12	-0.12 ; 0.36
	gamma 1 PAD vs. ACS	0.19	-0.13 ; 0.5
	gamma 0 2+ hospitalization vs. 1	-0.19	-0.42 ; 0.03
	gamma 0 IS vs. ACS	1.70	0.14 ; 3.26
	gamma 0 OTHERS CV vs. ACS	-0.56	-1.42 ; 0.3
	gamma 0 OTHERS NO CV vs. ACS	-0.63	-1.52 ; 0.25
	gamma 0 PAD vs. ACS	0.06	-1.08 ; 1.19
	gamma0 PCSK9-i 1 (Yes vs. No)	0.19	-0.07 ; 0.44

	gamma0 PCSK9-i 2+ (Yes vs. No)	-0.14	-0.55 ; 0.27

ASC=Acute Coronary Syndrome; CI=Confidence interval CV=Cardio Vascular; IS=Ischemic Stroke; LLT=Lipid-Lowering Therapy; PAD=Periphery Arterial Disease; PCSK9-I= Proprotein Convertase Subtilisin–Kexin type 9- Inhibitor;

Supplementary Table 6 Estimated parameters of all the transition hazards for the disease model for the subgroup analysis. The parameters are all adjusted for age, sex, Charlson Comorbidity index, the history of treatment with statins (duration and adherence) and the month/year eligibility date through IPTW.

Transition	Parameter	Estimate	95% CI
Toward death	gamma 0 2+ hospitalization vs. 1	0.62	0.24 ; 1.01
Toward death	gamma 0 IN-hospital vs. Out-of-hospital death	2.31	0.26 ; 4.36
Toward death	gamma 0 Out-of-hospital death	-0.47	-2.73 ; 1.78
Toward death	gamma 1 IN-hospital vs. Out-of-hospital death	-0.17	-0.85 ; 0.51
Toward death	gamma 1 Out-of-hospital death	1.71	1.02 ; 2.39
Toward death	gamma 2 IN-hospital vs. Out-of-hospital death	0.00	-0.02 ; 0.03
Toward death	gamma 2 Out-of-hospital death	0.09	0.05 ; 0.13
Toward death	gamma 3 Out-of-hospital death	-0.11	-0.15 ; -0.07
Toward death	Diabetes TOD+RF vs FH	0.59	-0.31 ; 1.49
Toward death	Diabetes TOD+RF+SP vs FH	0.54	-0.36 ; 1.43
Toward death	SP vs FH	0.06	-0.88 ; 0.99
Toward death	PCSK9-i (Yes vs. No)	-1.58	-1.99 ; -1.16
Towards hospital	gamma 0 2+ hospitalization vs. 1	3.06	2.9 ; 3.21
Towards hospital	gamma 0 ACS	-3.88	-4.58 ; -3.18
Towards hospital	gamma 0 IS vs. ACS	-1.82	-4.85 ; 1.21

Towards hospital	gamma 0 OTHERS CV vs. ACS	-0.01	-0.83 ; 0.81
Towards hospital	gamma 0 OTHERS NO CV vs. ACS	0.37	-0.49 ; 1.22
Towards hospital	gamma 0 PAD vs. ACS	-3.24	-6.42 ; -0.06
Towards hospital	gamma 1 ACS	0.38	0.26 ; 0.5
Towards hospital	gamma 1 IS vs. ACS	0.12	-0.47 ; 0.72
Towards hospital	gamma 1 OTHERS CV vs. ACS	0.00	-0.16 ; 0.16
Towards hospital	gamma 1 OTHERS NO CV vs. ACS	0.09	-0.08 ; 0.27
Towards hospital	gamma 1 PAD vs. ACS	0.03	-0.64 ; 0.71
Towards hospital	gamma 2 ACS	0.03	-0.01 ; 0.07
Towards hospital	gamma 2 IS vs. ACS	0.05	-0.08 ; 0.18
Towards hospital	gamma 2 OTHERS CV vs. ACS	-0.01	-0.06 ; 0.04
Towards hospital	gamma 2 OTHERS NO CV vs. ACS	0.01	-0.04 ; 0.06
Towards hospital	gamma 2 PAD vs. ACS	-0.15	-0.3 ; 0
Towards hospital	gamma 3 ACS	0.01	-0.12 ; 0.15
Towards hospital	gamma 3 IS vs. ACS	-0.34	-0.66 ; -0.03
Towards hospital	gamma 3 OTHERS CV vs. ACS	-0.10	-0.25 ; 0.06
Towards hospital	gamma 3 OTHERS NO CV vs. ACS	-0.01	-0.17 ; 0.15
Towards hospital	gamma 3 PAD vs. ACS	0.35	-0.03 ; 0.73
Towards hospital	gamma 4 ACS	-0.05	-0.32 ; 0.21
Towards hospital	gamma 4 IS vs. ACS	0.46	0.18 ; 0.74

Towards hospital	gamma 4 OTHERS CV vs. ACS	0.19	0.03 ; 0.36
Towards hospital	gamma 4 OTHERS NO CV vs. ACS	-0.01	-0.18 ; 0.17
Towards hospital	gamma 4 PAD vs. ACS	-0.27	-0.62 ; 0.08
Towards hospital	gamma 5 ACS	-0.09	-0.36 ; 0.19
Towards hospital	Diabetes TOD+RF vs FH	-0.46	-0.84 ; -0.07
Towards hospital	Diabetes TOD+RF+SP vs FH	0.58	0.22 ; 0.93
Towards hospital	SP vs FH	0.25	-0.12 ; 0.61
Towards hospital	PCSK9-i (Yes vs. No)	-0.18	-0.32 ; -0.04
Towards out-of-hospital	gamma 0 2+ hospitalization vs. 1	-0.19	-0.34 ; -0.04
Towards out-of-hospital	gamma 0 ACS	9.07	8.05 ; 10.1
Towards out-of-hospital	gamma 0 IS vs. ACS	0.92	-0.26 ; 2.11
Towards out-of-hospital	gamma 0 OTHERS CV vs. ACS	-0.30	-0.99 ; 0.39
Towards out-of-hospital	gamma 0 OTHERS NO CV vs. ACS	-0.85	-1.58 ; -0.12
Towards out-of-hospital	gamma 0 PAD vs. ACS	-0.30	-1.25 ; 0.64
Towards out-of-hospital	gamma 1 ACS	1.84	1.64 ; 2.04
Towards out-of-hospital	gamma 1 IS vs. ACS	0.41	0.1 ; 0.73
Towards out-of-hospital	gamma 1 OTHERS CV vs. ACS	0.07	-0.11 ; 0.24
Towards out-of-hospital	gamma 1 OTHERS NO CV vs. ACS	0.17	-0.03 ; 0.36
Towards out-of-hospital	gamma 1 PAD vs. ACS	0.10	-0.16 ; 0.35

Towards out-of-hospital	gamma 2 ACS	0.05	0.04 ; 0.06
Towards out-of-hospital	Diabetes TOD+RF vs FH	-0.43	-0.85 ; -0.01
Towards out-of-hospital	Diabetes TOD+RF+SP vs FH	-0.46	-0.85 ; -0.07
Towards out-of-hospital	SP vs FH	-0.44	-0.86 ; -0.03
Towards out-of-hospital	PCSK9-i (Yes vs. No)	0.15	-0.01 ; 0.32

ACS=Acute Coronary Syndrome; CV=Cardio Vascular; FH=Familiar Hypercholesterolemia; IS=Ischemic Stroke; LLT=Lipid-Lowering Therapy; TOD= Target Organ Damage; RF=Risk factor; PAD=Periphery Arterial Disease; PCSK9-I= Proprotein Convertase Subtilisin–Kexin type 9- Inhibitor; PDC=Proportion of Days Covered; PTCA= Percutaneous Transluminal Coronary Angioplasty; SP=Secondary Prevention.

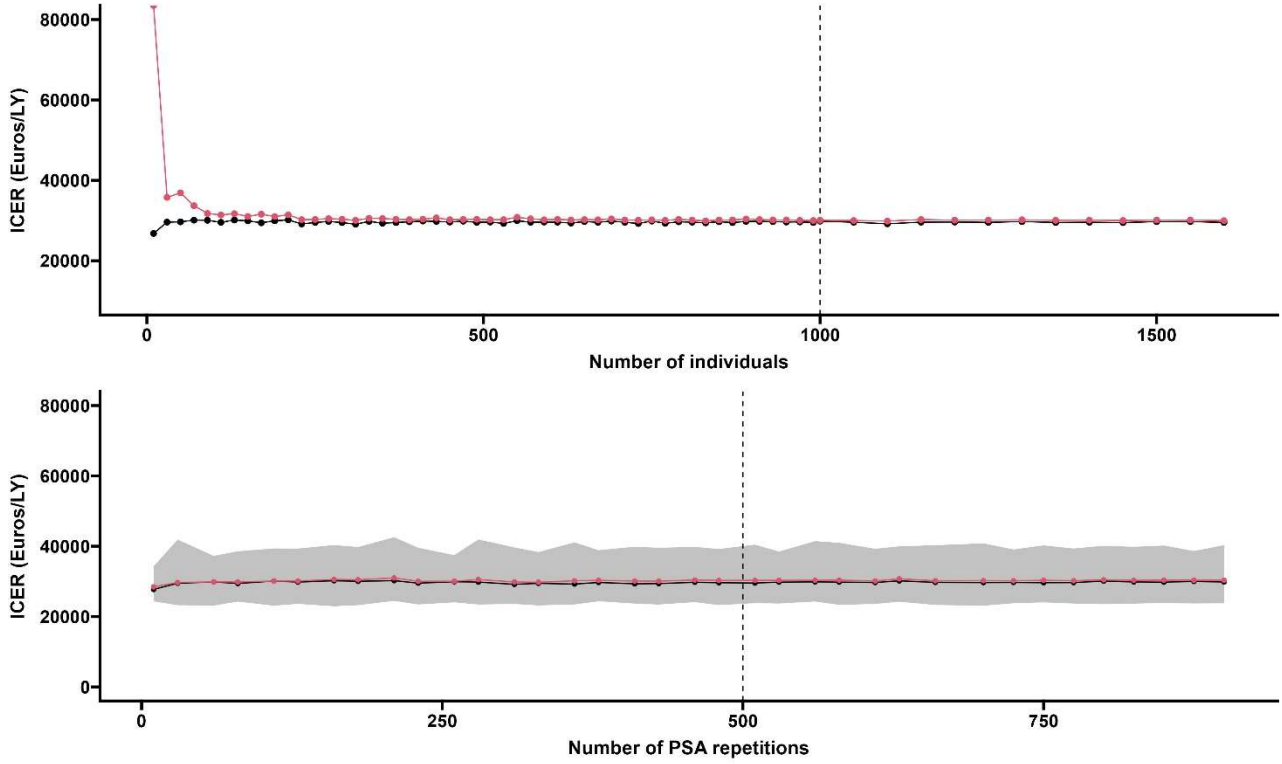
Supplementary Table 7 Results of the microsimulation economic model in the subgroup analysis

Eligibility Subgroup		**LLT (95% CI)**	**PCSK9-I+LLT (95% CI)**
FH (No ASCVD, No Diabetes TOD, No RF)	***Mean Utility* (years)**	16.4 (12.49,18.6)	19.62 (18.42,20.14)
	***Mean Costs*: Drugs (Euros)**	1772 (1350,2009)	86890 (81571,89180)
	***Mean Costs*: Hospitalizations length of stay below threshold (Euros)**	29380 (11620,78277)	25391 (11641,68736)
	***Mean Costs:* Hospitalizations extra days (Euros)**	8994 (3636,23404)	6705 (3121,17797)
Diabetes TOD + RF (No ASCVD)	***Mean Utility* (years)**	15.31 (14.05,16.55)	19.33 (18.51,19.81)
	***Mean Costs*: Drugs (Euros)**	1653 (1517,1787)	85571 (81943,87713)
	***Mean Costs*: Hospitalizations length of stay below threshold (Euros)**	10700 (6266,20534)	10749 (6092,21311)
	***Mean Costs:* Hospitalizations extra days (Euros)**	5350 (3174,8519)	4640 (2490,8150)
Only ASCVD	***Mean Utility* (years)**	14.75 (12.5,16.67)	19.39 (18.47,19.96)
	***Mean Costs*: Drugs (Euros)**	1593 (1350,1801)	85846 (81794,88370)
	***Mean Costs*: Hospitalizations length of stay below threshold (Euros)**	43895 (23936,92387)	43188 (24409 ,94110)
	***Mean Costs:* Hospitalizations extra days (Euros)**	22342 (12917,36488)	18778 (10623,32405)
Diabetes TOD+RF+ ASCVD	***Mean Utility* (years)**	10.25 (8.44,12.08)	17.73 (16.4,18.78)
	***Mean Costs*: Drugs (Euros)**	1107 (912,1304)	78530 (72601,83174)
	***Mean Costs*: Hospitalizations length of stay below threshold (Euros)**	55833 (34107 ,112660)	84041 (52472,173143)
	***Mean Costs:* Hospitalizations extra days (Euros)**	28161 (19289,43060)	37289 (24980,55984)

ASCVD=Atherosclerotic cardiovascular disease; FH=Familiar Hypercholesterolemia; LLT=Lipid-Lowering Therapy; TOD= Target Organ Damage; RF=Risk factor; PCSK9-I= Proprotein Convertase Subtilisin–Kexin type 9- Inibitor.

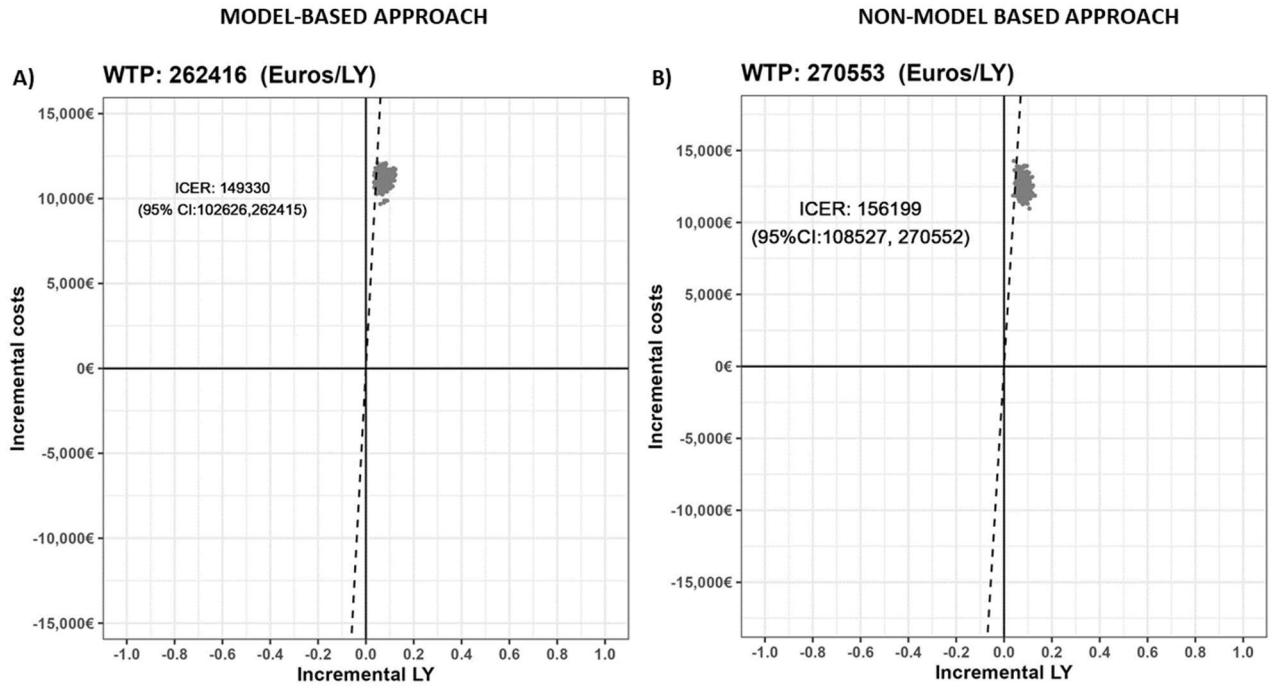
Supplementary Figure 1. Convergence diagnostics.

On the top, the ICER (Euros/LY) according to different number of individuals used in the timelife microsimulation. On the top, the ICER (Euros/LY) according to different number of PSA repetitions used in the lifetime microsimulation. The black line corresponds to the median and the red line correspond to the mean; the dashed area is the 95% CI. It can be observed that with 1000 individuals and 500 PSA repetitions convergence has been achieved.



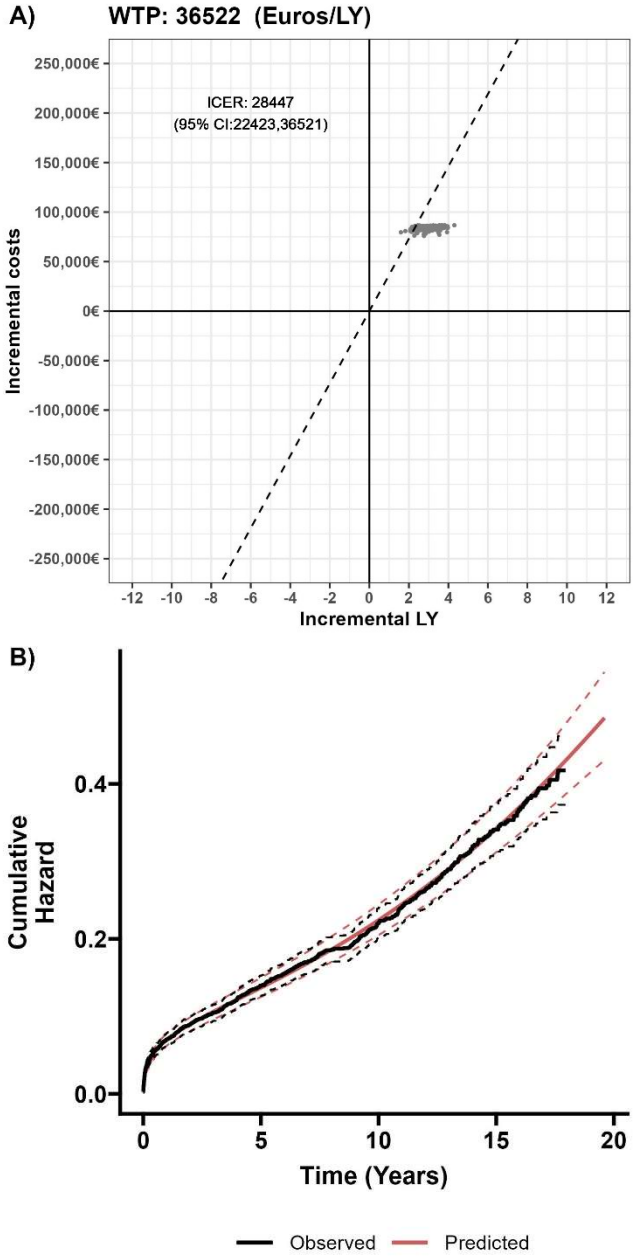
Supplementary Figure 2 Cost-effectiveness results on the short-term horizon.

On the left, Cost Effectiveness Plane and ICER (Euros/LY) with 95% on the short-term time horizon obtained with the model-based approach (Panel A). On the right, the corresponding ones obtained with the non-model based approach (Panel B) The dashed lines on the cost-effectiveness planes represent the minimum willingness to pay (wtp) per Life Year gained for the treatment to be considered cost-effective at 95% confidence level.



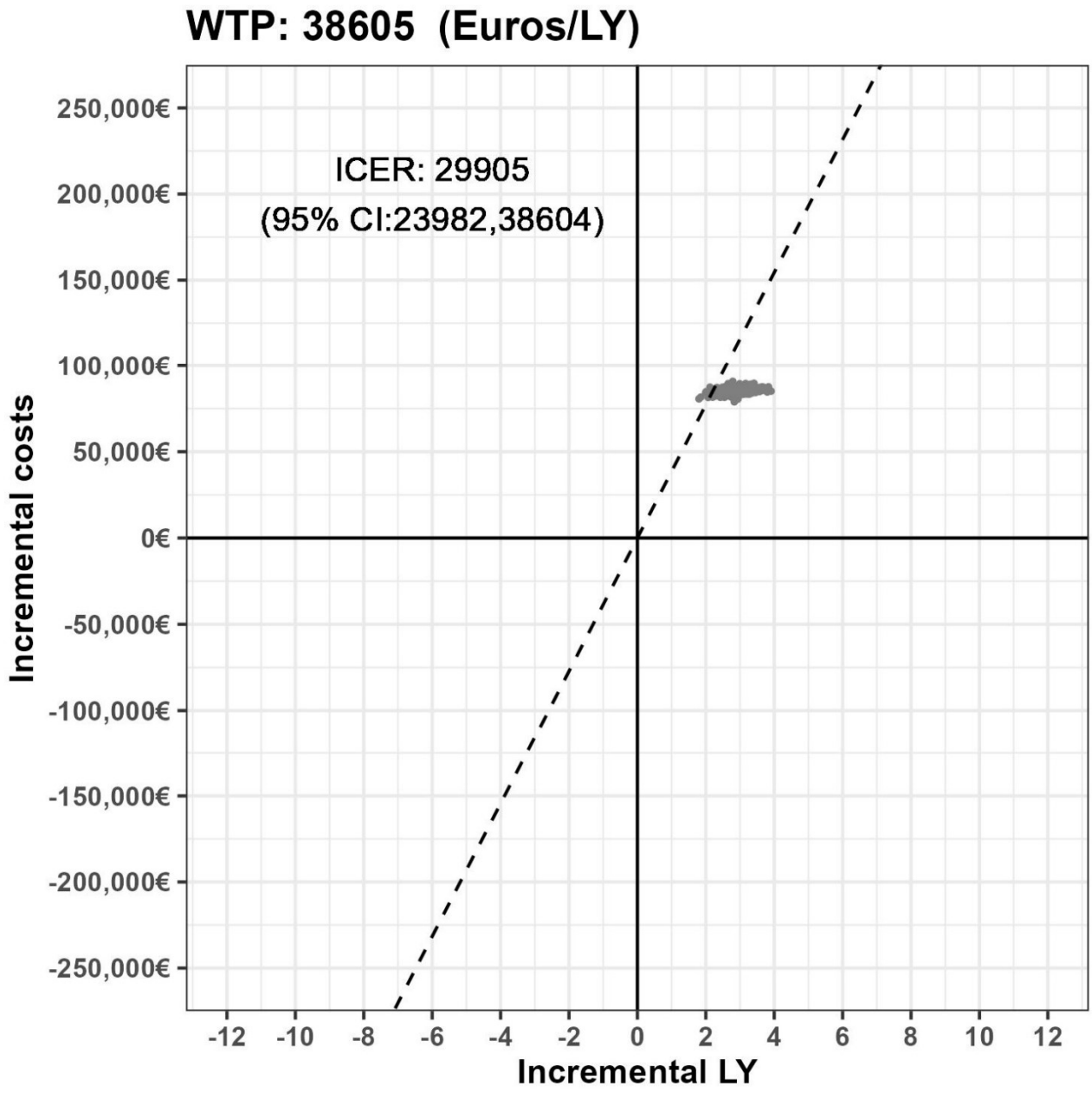
Supplementary Figure 3 Results of the sensitivity analysis A.

Panel A) *Cost Effectiveness Plane and ICER(Euros/LY) with 95% CI of the sensitivity analysis to assess the effect of extrapolating over maximum follow-up observed in data in lifetime microsimulation. The dashed lines on the cost-effectiveness planes represent the minimum willingness to pay(wtp) per Life Year gained for the treatment to be considered cost-effective at 95% confidence level. Panel B) Goodness-of fit for the long-term mortality rates comparing the cumulative hazard predicted from the disease-model for the standard LLT treatment (red) with the cumulative hazard observed in the historical cohort opportunely recalibrated (black).*



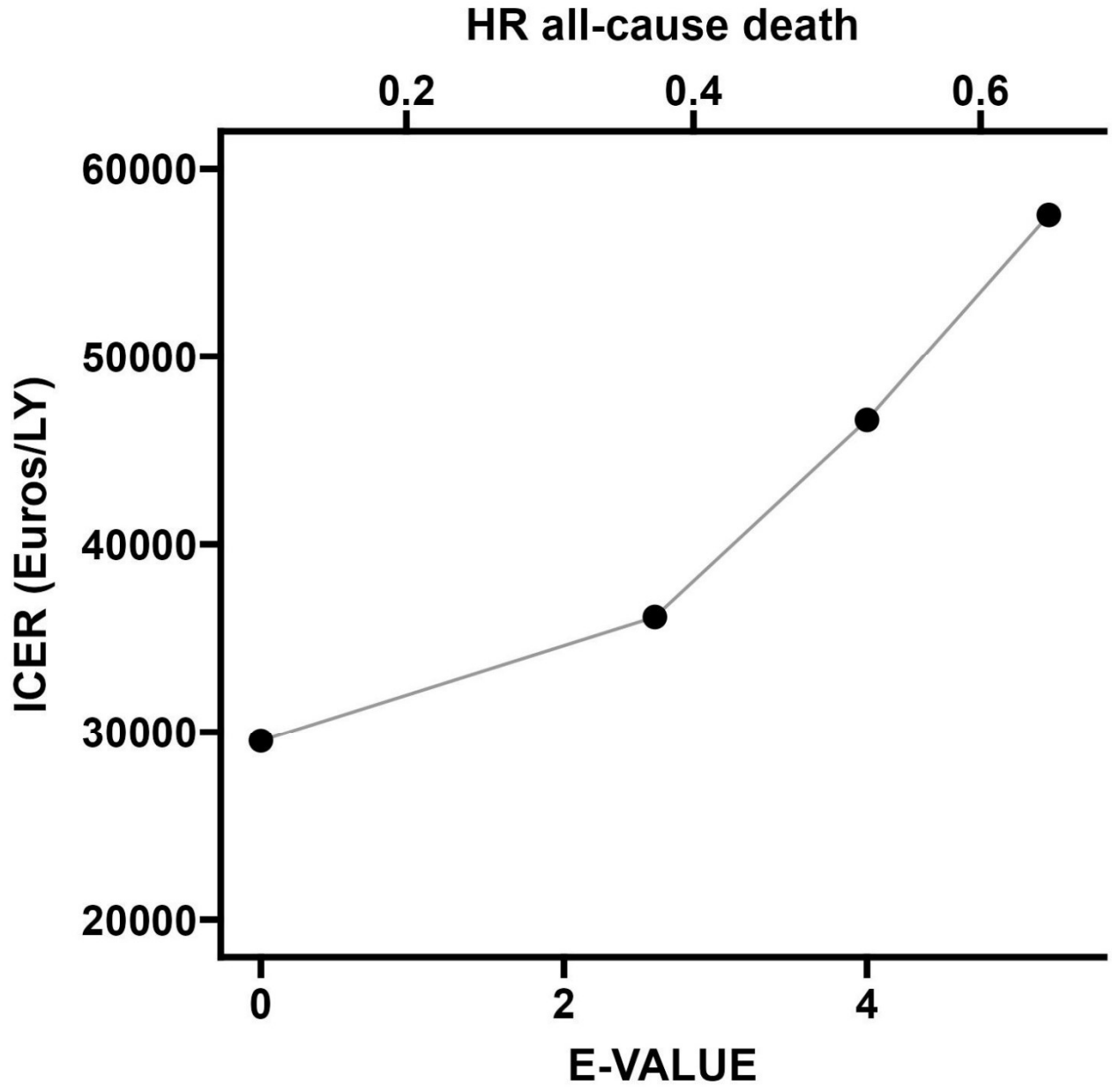
Supplementary Figure 4 Results of the sensitivity analysis B.

Cost Effectiveness Plane and ICER (Euros/LY) with 95% CI of the sensitivity analysis to assess the effect of 7% of individuals assigned to PCSK9 inhibitors been non-adherent in lifetime microsimulation. The dashed lines on the cost-effectiveness planes represent the minimum willingness to pay (wtp) per Life Year gained for the treatment to be considered cost-effective at 95% confidence level.



Supplementary Figure 5 Results of the sensitivity analysis C.

ICER (Euros/LY) obtained in the sensitivity analysis to assess the consequence of different scenarios regarding unmeasured confounding in the estimation of the effect of PCSK9 Inhibitor on death. The E-VALUE of 0 correspond to the case in which there is no unmeasured confounding and the HR on death is unbiased. E-VALUES greater than 0 correspond to cases in which the effect of the treatment is overestimated because of a set of unmeasured confounders. A E-VALUE equal to x means that there is a set of confounders that are associated with a x-fold increase in the risk of death, and that are x times more prevalent in treated than untreated subjects.



Supplementary Figure 6 Results of the sensitivity analysis D.

Cost Effectiveness Plane and ICER (Euros/QALY) with 95% CI. The dashed lines on the cost-effectiveness planes represent the minimum willingness to pay in Euros per QALY gained for the treatment to be considered cost-effective at 95% confidence level.