Cost-Effectiveness of Managing Familial Hypercholesterolemia Using Atorvastatin-Based Preventive Therapy

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Introduction and objectives. A cost-effectiveness model was developed to evaluate the efficiency of different preventive strategies in familial hypercholesterolemia (FH) in comparison with routine clinical practice (CP): atorvastatin monotherapy, 40 mg (A40) or 80 mg (A80), and atorvastatin combined with ezetimibe, 10 mg (A40+E10 or A80+E10).

Methods. A longitudinal population model with a time horizon for life-expectancy was developed within the context of the Spanish public healthcare system. Life tables for the Spanish population (2002) were modified using the standardized mortality rate for individuals with FH. Effectiveness was expressed in life-years gained (LYG), after taking into account reductions for risk (ie, Framingham risk score) and cardiovascular mortality. The costs (in 2005 terms) of the intervention (CI) and care (CC) were discounted at 6%, while effects were discounted at 3%.

Results. Routine CP, based on the Spanish FH registry: 1.97 LYG per patient versus no treatment; CI €5321, CC €23 389. A40: 2.59 LYG; reduction in CC compared with CP 4.5%; total costs (TC) €30 569. A80: 2.75 LYG; reduction in CC 6.4%; TC €30 133. A40+E10: 3.38 LYG; reduction in CC 14.3%; TC €36 104. A80+E10: 3.62 LYG; reduction in CC 17.6%; TC €35 317. From most to least efficient strategy, the incremental cost-effectiveness per LYG compared with CP was: *a)* A80: €1821; *b)* A40: €3012; *c)* A80+E10: €4021; and *d)* A40+E10: €5250.

Conclusions. Preventive treatment of FH with atorvastatin was cost-effective. The greatest cost-effectiveness was obtained with atorvastatin monotherapy, 80 mg. The addition of ezetimibe could produce further benefits at an acceptable incremental cost.

Key words: *Cost-effectiveness. Familial hypercholesterolemia. Atorvastatin.*

Coste-efectividad del manejo de la hipercolesterolemia familiar con estrategias de tratamiento preventivo basadas en atorvastatina

Introducción y objetivos. Evaluar la eficiencia de distintas estrategias preventivas en hipercolesterolemia familiar (HF) mediante un modelo de coste-efectividad de atorvastatina 40 mg y 80 mg en monoterapia (A40, A80) o combinado con ezetimiba 10 mg (A40+E10, A80+E10) respecto a la práctica clínica (PC).

Métodos. Modelo poblacional longitudinal, horizonte temporal: esperanza de vida. Perspectiva del SNS. Las tablas de vida de población española (2002) se modificaron con la tasa de mortalidad estandarizada (TME) para la población con HF. La eficacia se transformó, al disminuir el riesgo (tablas de riesgo de Framingham) y aminorar la mortalidad cardiovascular en años de vida ganados (AVG). Los costes (de 2005) de intervención (CI) y los costes de manejo (CM) se descontaron al 6% y los efectos, al 3%.

Resultados. En PC, según el Registro Español de HF: 1,97 AVG por paciente respecto a no tratar; CI, 5.321 euros, y otros CM, 23.389 euros. A40: 2,59 AVG, reducción del 4,5% del CM sobre PC, y coste total (COT), 30.569 euros. A80: 2,75 AVG, reducción del 6,4% del CM, y COT, 30.133 euros. A40+E10: 3,38 AVG, CM de 14,3% y COT, 36.104 euros. A80+E10: 3,62 AVG, reducción del 17,6% de CM y COT, 35.317 euros. De más a menos eficiente, el coste-efectividad incremental (CEI) por AVG extra respecto a PC: *a)* A80: 1.821 euros; *b)* A40: 3.012 euros; *c)* A80+E10: 4.021 euros, y *d)* A40+E10: 5.250 euros.

Conclusiones. El manejo preventivo de los pacientes con HF con atorvastatina es eficiente. La máxima eficiencia se consigue con atorvastatina 80 mg en monoterapia. Añadir ezetimiba puede producir un efecto adicional a un coste incremental aceptable.

Palabras clave: *Coste-efectividad. Hipercolesterolemia familiar. Atorvastatina.*

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ABBREVIATIONS

CP: clinical practice
FH: familial hypercholesterolemia
ICE: incremental cost-effectiveness
PYLL: potential years of life lost
SMR: standardized mortality rate
YLG: years of life gained

INTRODUCTION

Familial hypercholesterolemia (FH) is a hereditary problem that affects 1 in 400-500 people in the general population. It is caused by mutations in the gene coding for the receptor for low density lipoprotein and is transmitted in an autosomal dominant fashion. At least 50% of the first degree relatives of an affected person inherit the problem.[1] The importance of its diagnosis lies in the high incidence of premature cardiovascular disease[2,3] and the increased risk of cardiovascular death[4,5] with which it is associated, especially in people under 40 years of age.[4] It is estimated that if appropriate treatment is not provided, at least 50% of men and 20% of women with FH will suffer a coronary episode before 50 years of age.[2-4] There is now sufficient evidence to show that cardiovascular mortality and morbidity can be reduced by the use of statins in high risk patients with cardiovascular disease,[6-8] although for patients with FH such evidence is scarce.[9,10] However, it is probable that early diagnosis and adequate lipid lowering treatment could reduce these problems, especially in people under 60 years of age[9]; they are therefore highly recommendable with respect to this population.[11] Nonetheless, the high cost of statins and the lifetime treatment required render such primary prevention controversial from an economic point of view.

No studies have been published on the cost-effectiveness of lipid-lowering treatment in patients with FH. The aim of the present work was to determine the cost-effectiveness of different therapeutic strategies for the prevention of cardiovascular disease in patients with FH, using a model comparing atorvastatin alone, or in combination with ezetimibe, with normal clinical practice (CP).

METHODS

Design

This study involved a longitudinal populational cost-effectiveness model with life expectancy as the time horizon. The study subjects were a cohort of patients diagnosed with FH showing the same profile as recorded in the Spanish FH Registry.[2] A preventive lifetime lipid-lowering intervention for the reduction of cardiovascular risk, composed of 5 alternative treatments, was analyzed from the viewpoint of the Spanish health system.

Patients

The patient cohort was simulated from the data for patients included in the Spanish FH Registry[2] with a genetic diagnosis of FH and for whom sociodemographic, physiological, lifestyle, cardiovascular background, comorbidity, and treatment information was complete. The final sample included 881 patients, 44% of whom were men. The mean age of patients was 48 (18-82) years.

Intervention

Patients received 1 of the following lipid-lowering treatments for the reduction of cardiovascular risk: *a)* CP as detailed in the Registry (Table 1 shows the different statins used and their clinical doses according to normal clinical practice for the years covered by the Registry [1999-2002]); *b)* atorvastatin 40 mg alone (A40); *c)* atorvastatin 40 mg plus ezetimibe 10 mg (A40+E10); *d)* atorvastatin 80 mg alone (A80); or *e)* atorvastatin 80 mg plus ezetimibe 10 mg (A80+E10).

Model

Actuarial methodology was used to calculate the potential years of life lost (PYLL) due to cardiovascular disease with respect to cardiovascular risk. For each patient the annual costs of treatment were imputed, as well as the costs corresponding to the consumption of resources used in the management of cardiovascular complications. Figure 1 shows the rationale of the model; Figure 2 describes the model in detail.

Effectiveness

Using life tables for the Spanish population, life expectancy was calculated taking into account the sex and age group of all patients in the sample as though they belonged to the general population.[12,13] In the determination of the PYLL due to FH it was assumed that: *a)* the increase in all-cause mortality was due to increased cardiovascular mortality, and that the distribution of deaths of other cause was no different to that seen in the general population; *b*) the genetic defect associated with FH is expressed over the lifetime of the patient; therefore, the different distribution of mortality with respect to the general population is the same in carriers of both sex and for each age group; *c)* the different all-cause mortality of the FH patients compared to the general population is obtainable by assuming a standardized mortality rate (SMR) per age group and sex of 1.59 (95%

TABLE 1. **Treatment Received According to Normal Clinical Practice by Patients Included in the Spanish Familial Hypercholesterolemia Registry (Percentages)**

	Statin Alone	With Resins	Total
Atorvastatin			
10 mg	9.7	1.5	11.2
20 mg	9	2.5	11.4
30 mg	1.8	0.9	2.7
40 mg	4.8	2.6	7.4
50 mg	0.1	0.1	0.2
60 mg	0.9	0.2	1.1
80 mg	1.2	0.6	1.8
Total	27.5	8.3	35.9
Cerivastatin			
0.2 mg	3.1	0.3	3.4
0.4 mg	0.9	0.2	1.1
0.6 mg	0.1	0.3	0.4
0.8mg	0.1		0.1
Total	4.2	0.7	4.9
Fluvastatin			
20 mg	0.2		0.2
40 mg	0.5	0.1	0.6
Total	0.7	0.1	0.8
Lovastatin			
10 mg	0.1		0.1
20 mg	0.9	0.1	1
40 mg	0.5	0.1	0.5
60 mg	0.1		0.1
80 mg	0.1		0.1
120 mg		0.1	0.1
Total	1.6	0.3	1.9
Pravastatin			
10 mg	0.5		0.5
20 mg	1.1	0.2	1.3
40 mg	1.4	0.5	1.8
60 mg	0.1		0.1
80 mg	0.1		0.1
Total	3.2	0.6	3.8
Simvastatin			
10 mg	2.3		2.3
20 mg	10	1.6	11.6
30 mg	0.3	0.2	0.5
40 mg	9.7	4.7	14.4
50 mg	0.1		0.1
60 mg	0.6	0.6	1.3
80 mg	1.1	1.3	2.4
120 mg		0.1	0.1
Total	24.1	8.5	32.6
No treatment			20

confidence interval [CI], 1.07-2.26)[5]; and *d)* once the all-cause and cardiovascular mortality of the general population is known,[13] plus the SMR for the FH population, the different mortality of the FH patients can be calculated, along with their cardiovascular mortality, their life expectancy, and PYLL without treatment, compared to the general population.[14] Table 2 shows the results of these calculations.

The effect of treatment was estimated by the reduction from the initial cardiovascular risk (CVR_0) resulting from the reduction in low density lipoprotein cholesterol (LDL-C). The cardiovascular risk of each patient was calculated using the Framingham Heart Study[15] equations for primary and further events. The LDL-C-lowering effect of the therapeutic statins was obtained from efficacy data in the literature.[16] The cardiovascular risk modified by treatment (CVR_1) allowed the estimation of the reduction in relative risk in the form of a coefficient (CVR_1/CVR_0) corresponding to a reduced probability of cardiovascular death over the next 5 years. Since the treatments followed were lifetime treatments, and since the probability of cardiovascular death was reduced in each of the 5 year periods until the end of life expectancy, the probability of all-cause death must also fall, thus modifying life expectancy. It was also assumed that treatment with statins until the end of life has a constant effect independent of age, and that no patients abandoned treatment.

The majority of the patients in the Registry had been prescribed a lipid-lowering treatment. The modified life expectancy of each was therefore calculated on the basis of the therapeutic efficacy of the treatment received according to data in the literature.[16] The difference between the PYLL with and without intervention in each subject represents the number of years of life gained (YLG) with CP. This process was repeated to calculate the YLG associated with each treatment option in the intervention. In order to express the results as present-day values, a discount rate of 3% per year on the PYLL[17] was assumed.

COSTS

Total costs were deemed to be the cost of the intervention plus the costs of managing FH and potential cardiovascular events. The intervention costs were obtained as the sum of the annual costs of treatment until the end of life expectancy. The annual cost per patient was €573.31 for A40, €1117.63 for A40+E10, €573.12 for A80, and €1117.44 for A80+E10. The costs of CP per patient were calculated from the treatment costs for the established doses over 1 year as shown in the Registry, always assuming the use of the most cost-effective commercial products.

The costs of managing FH were calculated assuming a consumption of assistance resources (medical and hospital assistance), diagnostic tests, and the pharmacological management of cardiovascular events. The resources used per patient/year depended on the incidence of cardiovascular events, the type of such events (myocardial infarction, other ischemic heart disease, ictus, heart failure), and their lethality.

Cardiovascular complications were simulated from the epidemiological profile of cardiovascular diseases for the Spanish population[18,19]; each patient was attributed,

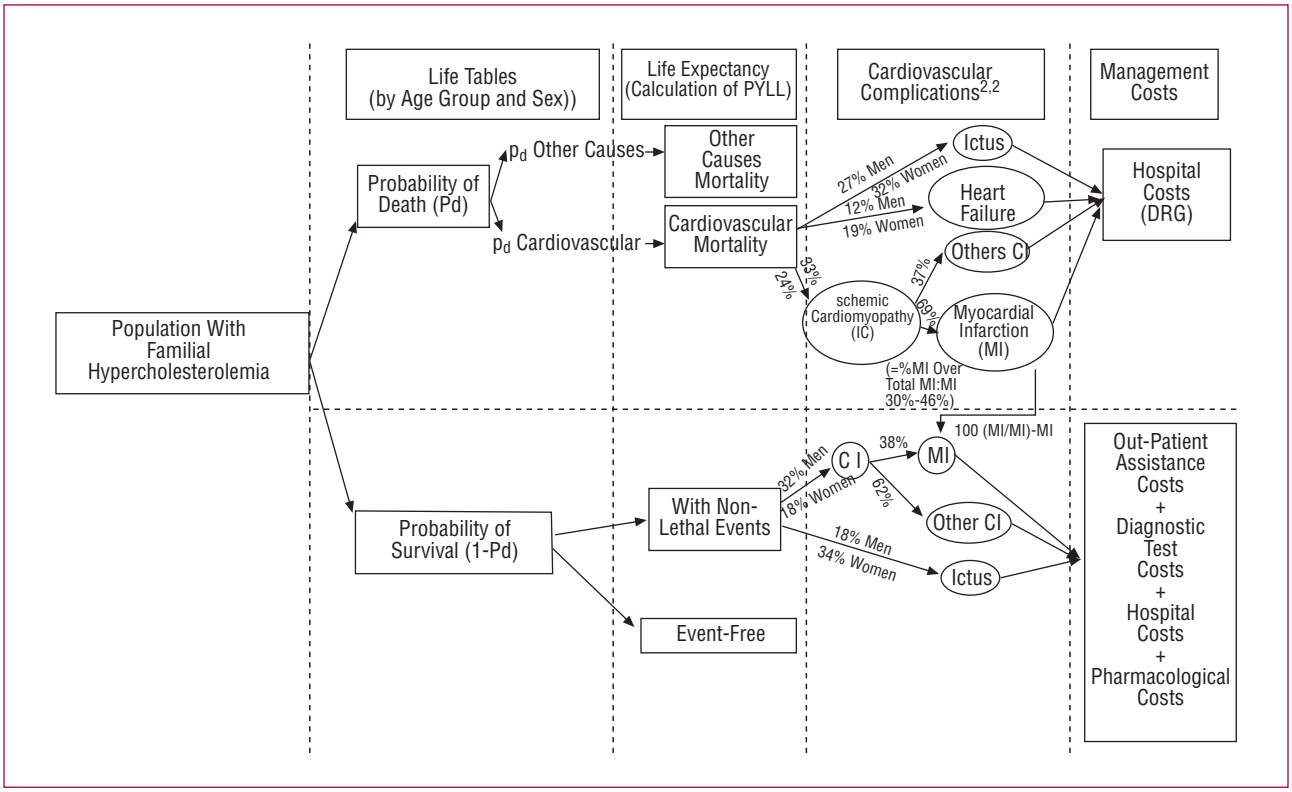

Figure 1. Rationale of the model.

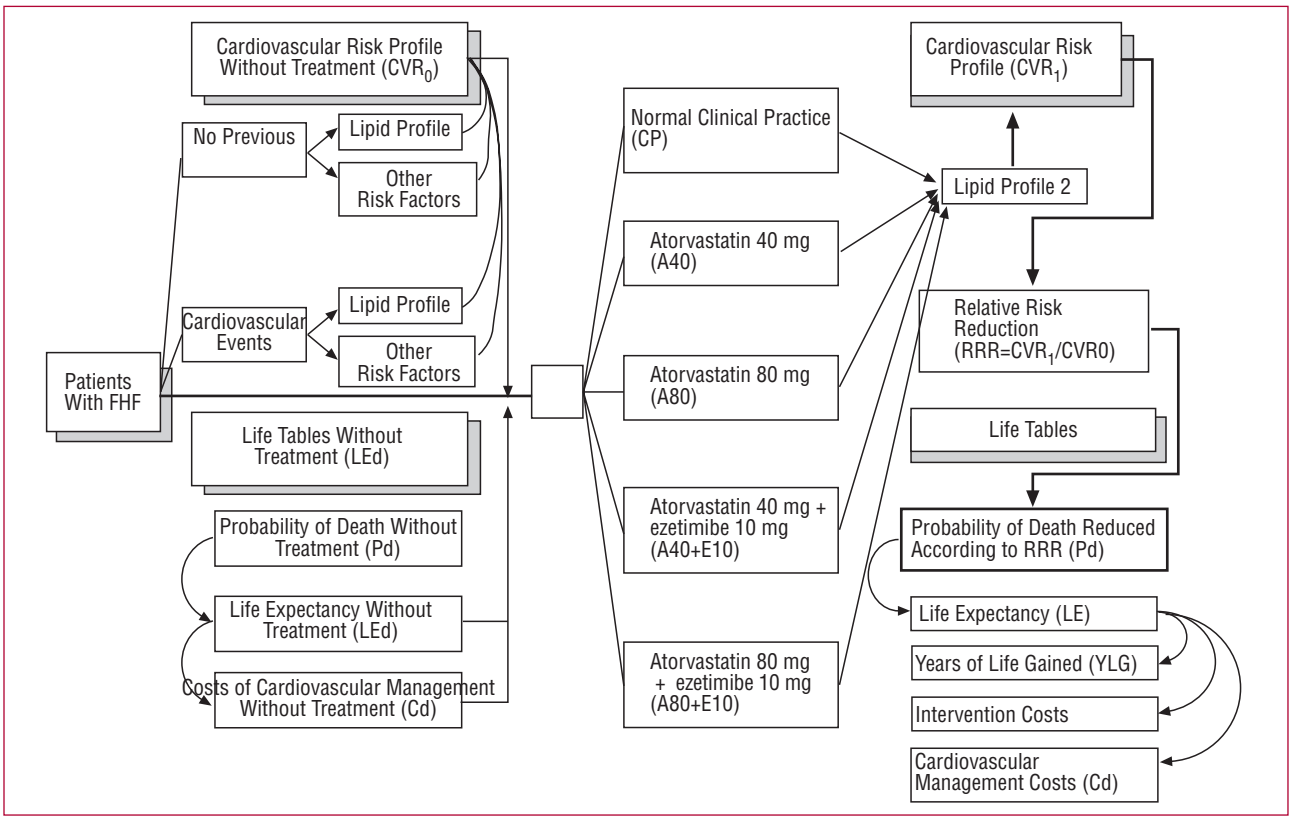

Figure 2. Structure of the cost-effectiveness model.

TABLE 2. **Mortality and Potential Years of Life Lost Due to Cardiovascular Reasons in Patients With Familial Hypercholesterolemia Having Received no Prior Treatment**

Age Group	General Population			Baseline Scenario in the FH Population With no Preventive Treatment (SMR=1.59)				Worst Case Scenario in the FH Population Without Preventive Treatment (SMR=1.07)				Best Case Scenario in the FH Population Without Preventive Treatment (SMR=2.26)			
	All-Cause Mortality, %	Cardiovascular Mortality, %	Mortality Due to Other Causes, %	All Cause Mortality, %	Cardiovascular Mortality, %	Mortality Due to Other Causes, %	Potential Years of Life Lost	All-Cause Mortality, %	Cardiovascular Mortality %	Mortality Due to Other Causes, %	Potential Years of Life Lost	All Cause Mortality, %	Cardiovascular Mortality, %	Mortality Due to Other Causes, %	Potential Years of Life Lost
Both sexes															
15-19	0.04	0.00	0.04	0.06	0.02	0.04	9.4	0.04	0.00	0.04	4.9	0.09	0.05	0.04	13.3
20-24	0.05	0.00	0.05	0.08	0.03	0.05	9.3	0.05	0.00	0.05	4.9	0.11	0.06	0.05	13.2
25-29	0.05	0.00	0.05	0.09	0.03	0.05	9.3	0.06	0.01	0.05	4.9	0.12	0.07	0.05	13.1
30-34	0.07	0.00	0.06	0.11	0.04	0.06	9.2	0.07	0.01	0.06	4.9	0.15	0.09	0.06	12.9
35-39	0.11	0.01	0.10	0.17	0.07	0.10	9.1	0.11	0.02	0.10	4.9	0.24	0.14	0.10	12.8
40-44	0.15	0.02	0.13	0.24	0.11	0.13	9.0	0.16	0.03	0.13	4.9	0.34	0.21	0.13	12.6
45-49	0.24	0.04	0.21	0.38	0.18	0.21	8.9	0.26	0.05	0.21	4.8	0.55	0.34	0.21	12.3
50-54	0.36	0.05	0.31	0.58	0.27	0.31	8.7	0.39	0.08	0.31	4.8	0.82	0.51	0.31	12.0
55-59	0.52	0.09	0.44	0.83	0.40	0.44	8.5	0.56	0.12	0.44	4.8	1.18	0.75	0.44	11.6
60-64	0.75	0.13	0.62	1.20	0.57	0.62	8.2	0.81	0.18	0.62	4.7	1.70	1.08	0.62	11.1
65-69	1.30	0.27	1.03	2.07	1.04	1.03	8.0	1.39	0.36	1.03	4.6	2.94	1.91	1.03	10.6
70-74	2.02	0.47	1.55	3.21	1.66	1.55	7.6	2.16	0.61	1.55	4.6	4.57	3.02	1.55	9.9
75-79	3.53	0.95	2.58	5.61	3.04	2.58	7.2	3.78	1.20	2.58	4.5	7.98	5.40	2.58	9.1
80-84	6.25	1.92	4.33	9.94	5.61	4.33	6.8	6.69	2.36	4.33	4.4	14.13	9.80	4.33	8.3
85 and above	14.57	5.21	9.36	23.17	13.81	9.36	6.4	15.59	6.23	9.36	4.3	32.94	23.58	9.36	7.6
Men															
15-19	0.05	0.00	0.05	0.09	0.03	0.05	8.8	0.06	0.01	0.05	4.2	0.12	0.07	0.05	13.0
20-24	0.07	0.00	0.07	0.12	0.05	0.07	8.8	0.08	0.01	0.07	4.1	0.17	0.10	0.07	12.9
25-29	0.08	0.00	0.07	0.12	0.05	0.07	8.7	0.08	0.01	0.07	4.1	0.18	0.10	0.07	12.7
30-34	0.09	0.01	0.09	0.15	0.06	0.09	8.6	0.10	0.01	0.09	4.1	0.21	0.12	0.09	12.5
35-39	0.15	0.01	0.14	0.24	0.10	0.14	8.5	0.16	0.02	0.14	4.1	0.34	0.20	0.14	12.3
40-44	0.21	0.03	0.18	0.33	0.15	0.18	8.4	0.22	0.04	0.18	4.1	0.47	0.29	0.18	12.1
45-49	0.34	0.06	0.28	0.54	0.26	0.28	8.2	0.36	0.08	0.28	4.1	0.76	0.48	0.28	11.8
50-54	0.52	0.09	0.43	0.82	0.39	0.43	8.0	0.55	0.12	0.43	4.0	1.17	0.74	0.43	11.4
55-59	0.76	0.14	0.62	1.21	0.59	0.62	7.7	0.82	0.20	0.62	3.9	1.72	1.10	0.62	10.8
60-64	1.10	0.20	0.90	1.75	0.85	0.90	7.3	1.18	0.28	0.90	3.8	2.49	1.59	0.90	10.2
65-69	1.91	0.41	1.50	3.04	1.53	1.50	7.0	2.04	0.54	1.50	3.7	4.32	2.81	1.50	9.5
70-74	2.87	0.65	2.23	4.57	2.34	2.23	6.5	3.07	0.85	2.23	3.5	6.49	4.26	2.23	8.7
75-79	4.88	1.22	3.66	7.75	4.09	3.66	5.9	5.22	1.56	3.66	3.4	11.02	7.36	3.66	7.8
80-84	8.16	2.22	5.94	12.98	7.04	5.94	5.4	8.73	2.79	5.94	3.2	18.45	12.51	5.94	6.8
85 and above	16.62	5.08	11.54	26.43	14.88	11.54	4.9	17.78	6.24	11.54	3.0	37.56	26.02	11.54	6.0
Women															
15-19	0.02	0.00	0.02	0.04	0.01	0.02	9.4	0.02	0.00	0.02	5.4	0.05	0.03	0.02	12.7
20-24	0.02	0.00	0.02	0.04	0.02	0.02	9.3	0.03	0.00	0.02	5.4	0.06	0.03	0.02	12.7
25-29	0.03	0.00	0.03	0.04	0.02	0.03	9.3	0.03	0.00	0.03	5.4	0.06	0.04	0.03	12.6
30-34	0.04	0.00	0.04	0.06	0.02	0.04	9.3	0.04	0.00	0.04	5.4	0.09	0.05	0.04	12.5
35-39	0.06	0.00	0.06	0.09	0.04	0.06	9.2	0.06	0.01	0.06	5.4	0.13	0.08	0.06	12.4
40-44	0.10	0.01	0.09	0.15	0.06	0.09	9.2	0.10	0.01	0.09	5.4	0.22	0.13	0.09	12.3
45-49	0.15	0.01	0.13	0.23	0.10	0.13	9.1	0.16	0.02	0.13	5.4	0.33	0.20	0.13	12.1
50-54	0.21	0.02	0.19	0.33	0.14	0.19	9.0	0.22	0.04	0.19	5.4	0.47	0.28	0.19	11.9
55-59	0.29	0.03	0.26	0.47	0.21	0.26	8.9	0.31	0.05	0.26	5.4	0.66	0.40	0.26	11.6
60-64	0.42	0.06	0.36	0.67	0.31	0.36	8.7	0.45	0.09	0.36	5.4	0.96	0.60	0.36	11.3
65-69	0.77	0.15	0.62	1.22	0.60	0.62	8.5	0.82	0.20	0.62	5.3	1.74	1.12	0.62	11.0
70-74	1.32	0.33	0.99	2.10	1.10	0.99	8.3	1.41	0.42	0.99	5.3	2.98	1.99	0.99	10.5
75-79	2.55	0.76	1.79	4.06	2.27	1.79	8.0	2.73	0.94	1.79	5.2	5.77	3.98	1.79	10.0
80-84	5.09	1.74	3.35	8.10	4.74	3.35	7.6	5.45	2.10	3.35	5.1	11.51	8.16	3.35	9.3
85 and over	13.70	5.27	8.43	21.78	13.35	8.43	7.3	14.66	6.23	8.43	5.0	30.96	22.53	8.43	8.6

FH indicates familial hypercholesterolemia; SMR, standardized mortality rate.

TABLE 3. **DRG Codes Used in the Management of Each Complication and the Relative Frequencies of Each Complication in Spain in 2000**

Complication	DRG Code	Cost per DRG (BOCM) 2005[21]	Cost per DRG (DOGV) 2005[22]	No. (2000)[20]	Relative Frequency of Each Complication	Hospital Management Costs
Ischemic cardiomyopathy	132	3123	2427	783	0.03	
	133	1884	1788	1832	0.06	
	134	2168		1608	0.05	
	140	2228	1996	13 035	0.42	
	141	2212		1176	0.04	
	142	1858	1564	2463	0.08	
	144	3509	2866	2108	0.07	4874
	145	2532	2033	2025	0.07	
Codes shared by ischemic cardiomyopathy and myocardial infarction	546	19 900	19 372	495	0.02	
	106	16 952		543	0.02	
	107	16 504		1005	0.03	
	112	4258	3919	7323	0.24	
	120	9241	5848	793	0.03	
	550	11 677		1568	0.05	
Myocardial infarction	121	6099	4568	3891	0.19	
	122	4440	4090	7000	0.34	
	123	5173	3441	1770	0.09	8355
	808	7428	6365	1797	0.02	
Codes shared by ischemic cardiomyopathy and myocardial infarction	546	19 900	19 372	495	0.03	
	106	16 952		543	0.05	
	107	16 504		1005	0.36	
	112	4258	3919	7323	0.04	
	120	9241	5848	793	0.08	
	550	11 677		1568	0.05	
Congestive heart failure	124	3513	3241	3583	0.09	3018
	125	2181	2004	8250	0.21	
	127	2702	2698	17 615	0.46	
	544	4176	5604	9237	0.24	
Ictus	14	3423	2759	15 942	0.48	
	15	2037	2039	8901	0.27	
	16	3291	3314	423	0.01	3742
	17	1958	1925	837	0.03	
	532	4923	4085	1201	0.04	
	533	7526	5795	4991	0.15	
	5	5937	4860	750	0.02	

BOCM indicates official bulletin of the Spanish autonomous communities; DOGV, official bulletin of the Valencian regional government.

for his/her remaining years of life, the consumption of resources corresponding to the sum of those necessary to manage each fraction contemplated in this profile, weighted by populational prevalence. Figure 1 describes the annual fractions considered and their weight in the cost of management.

The information used to establish the resources consumed in the management of events was obtained by consultation with experts of different specialties. It was assumed that lethal events consumed hospital resources alone. Non-lethal events were understood to also consume extra-hospital resources. The hospital resources were obtained from combined clinical management groups, diagnosis-related groups (DRG). The hospital management costs of a complication were calculated as the sum of the DRG costs weighted by frequency[20] (Table 3). Table 4 shows the resources and medical costs taken into account.[21-24] Table 5 shows the pharmacological resources used, estimated from information supplied by experts and the calculation of the annual consumption necessary for each group of medications according to the prescriptions made and their price (extracted from different databases).[25,26] Table 6 shows the total annual costs of managing FH and cardiovascular events.

All prices were adjusted to their costs in Spain in 2005. A 6% annual discount on these costs was taken into account.[27]

TABLE 4. **Medical Resources Consumed, Their Price, and Source of Informatio**

Setting	Indication	Consumption of Resources	Price per Unit, €	Source
Consultations				
Primary attention	All patients	5 per year without events, 10 with events	46.31	21-23
Specialist attention	All patients	2 per year without events. 3 with events	138.33	21-23
Emergencies				
Hospital emergency		0.012 per year in patients without events	112.48	21-24
Diagnostic tests	All patients			
Baseline tests	All patients	3 per year	56.77	23
Blood tests	All patients	1 per year	23.16	24
Electrocardiogram	All patients	1 per year	7.36	22
Related to an event (additional)				
Coronary angiography	IC, MI, CHF	1 per year	889.52	22
Ergometry	IC. MI	1 per year	45.15	22
Electrocardiogram	All patients	1 per year	7.36	22
Echocardiography	All patients	1 per year	117.8	22
PET	MI	1 per year	1290	21
Chest x-ray	IC. MI	1 per year	13.65	22
CT	Ictus	1 per year	107.14	22
Doppler	Ictus	1 per year	73.64	22
Echo-Doppler	Ictus	1 per year	72.65	22

CHF, congestive heart failure; CT, computed tomography; IC indicates ischemic cardiomyopathy; MI, myocardial infarction; PET, positron emission tomography.

Sensitivity

Scenario analyses were performed with respect to SMR[3]: *a)* baseline scenario: central estimate for SMR and mean value of costs; *b)* best case scenario: upper limit of SMR and management costs 10% lower; and *c)* worst case scenario: lower limit of SMR and management costs 10% higher. A sensitivity analysis was also performed in which the discount rate for both costs and results was 6%.

RESULTS

Table 7 shows the results for costs and effectiveness.

Baseline Scenario

Assuming an SMR in FH of 1.59 with respect to the general population, the PYLL expected are 7551 (8.6 [interval, 5.4-9.4])/patient).

Treating with CP compared to no treatment led to an improvement (after the annual discount of 3%) of 1.97 (0-4.75) YLG. The cost of intervention (after the annual discount of 6%) was €5321 (0-41350), and of management €23 389 (13 686-54 505); the latter made up 81.5% of the total €28 710 (14 206-56 183).

With A40, the YLG compared to no treatment was 2.59 years (1.19-4.05). The cost of intervention per patient was €8237 (2560-9899) and of management €22 333 (13 412-49 459), 4.5% less than with CP. The total cost was €30 569 (23 311-53 931).

Treatment with A40+E10 was associated with a YLG/patient of 3.38 (1.67-5.16) with respect to no treatment. The cost of intervention per treatment was €16 057 (4990-19 297) and of management €20 047 (13 026-44 420), 14.3% less than with CP. The total cost was €36 104 (25 837-54 703).

Treatment with A80 was associated with a YLG/patient of 2.75 (1.29-4.29), an intervention cost of €8234 (2559-9896), and a management cost of €21 899 (13 339-48 572), 6.4% less than with CP. The total cost was €30 133 (23 235-53 044).

Treatment with A80+E10 was associated with a YLG/patient of 3.62 (1.82-5.48) with respect to no treatment. The intervention cost was €16 054 per patient (4990-19 294) and the management cost €19 262 (12 891-42 453), 17.6% less than with CP. The total cost per patient with this treatment was €35 317 (24 477-53 778).

Table 8 shows the results for effectiveness, costs, and efficiency for the different treatments and CP.

Treatment with A40 was associated with a YLG/patient of 0.62 for an additional cost of €1859/patient with respect to CP, an incremental cost-effectiveness (ICE) of €3012/YLG. Treating with A40+E10 added 1.41 YLG/patient and cost €7394 more than CP, resulting in an ICE of €5250/YLG. With A80 a mean 0.78 YLG/patient were gained over CP at an additional cost of €1423, resulting in an ICE of €1821/YLG. Finally, with A80+E10 the gain was 1.64 YLG/patient, at a cost of €6607 more than with CP, resulting in an ICE of €4021/YLG.

Sensitivity Analysis

The most unfavorable scenario was that when general and cardiovascular mortalities were similar to that of the

TABLE 5. **Pharmacological Resources Consumed, Their Price, and Method of Calculation**

Treatment Drugs	Ischemic Cardiomyopathy		Myocardial Infarction		Heart Failure		Ictus		Calcultion	Components	Unit
	Percentage of Patients Consuming	Mean Annual Price, €	Percentage of Patients Consuming	Mean Annual Price, €	Percentage of Patients Consuming	Mean Annual Price, €	Percentage of patients Consuming	Mean Annual Price, €			
Diuretics	0.200	16.51	0.200	16.51	1.000	16.51	0.200	16.51	MWSV	Hydrochlorothiazide 12.5 mg/day Furosemide 40 mg Spironolactone 25 mg Indapamide 2.5 mg/day	NA
Aspirin	1.000	29.40	1.000	29.40	1.000	29.40	1.000	29.40	GPB	100 mg/day	2.45
Clopidogrel	1.000 3-6 (4.5) months	267.75	1.000 3-6 (4.5) months	267.75	0.000	0.000	0.000	0.000	PGA		59.5
Beta-blockers	1.000	91.45	1.000	91.45	0.086	91.45	0.086	91.45	MWSV	Atenolol 50 mg/day Carvedilol 25 mg/day	NA
Calcium channel inhibitors	0.781	256.4	0.781	256.4	0.781	256.4	1.000	256.4	MWSV	Amlodipine 10 mg/day Diltiazem 180 mg/day Verapamil 240 mg/day	NA
Alpha-blockers	0.205	202.56	0.205	202.56	0.205	202.56	0.205	202.56	PRA	Doxazosin 4 mg/day	16.88
ACEi	0.660	84.62	0.660	84.62	0.660	84.62	0.660	84.62	MWSV	Enalapril 20 mg/day Lisinopril 20 mg/day Perindopril 4 mg/day Trandolapril 2 mg/day	NA
ARA-II	0.330	313.46	0.330	313.46	0.330	313.46	0.330	313.46	MWSV	Irbesartan 150 mg/day Losartan 50 mg/day Valsartan 160 mg/day Candesartan 32 mg/day	NA
Gastrointestinal	0.046	438.24	0.046	438.24	0.046	438.24	0.046	438.24	WMOPP (GBP-RP)	Antacids (4.2%) Anti-ulceratives (4.8%) Anti-spasmodic drugs (4.9%)	3.79 13.62 5.67

ACEi indicates, angiotensin converting enzyme inhibitors; DRG, diagnosis-related groups; GPB, price of boxes of generic medication for covering mean daily dose for 1 year; MWSV, mean weighted by sales volume of the price needed to cover the mean daily dose for 1 year (2005). This is obtained in each pharmacological group for the number of boxes of drugs of each kind of presentation on the market weighted by their sales numbers; RP, reference price of boxes of drugs needed to cover mean daily dose for 1 year; WMOPP (GBP-RP), indicates weighted mean obtained from the probability of prescription, ie, mean price of boxes (generic or reference price) needed to cover the needs of the mean daily dose for 1 year, weighted by the probability of prescription obtained from the literature*;
*Evans JMM, MacDonald TM, Leese GP, Ruta DA, Morris AD. Impact of type 1 and type 2 diabetes on patterns and costs of drug prescribing. Diabetes Care. 2000;23:770-7.

TABLE 6. **Costs (in Euros) of Resource Consumption for the Management of Patients With Familial Hypercholesterolemia Excluding Pharmacological Treatment**

Patients free of events	710.37	
Patients with events		
	Non-lethal	Lethal
Ischemic cardiomyopathy	8230.79	5584.78
Infarction	13 000.91	9064.89
Heart failure	6015.49	3728.33
Ictus	6140.10	4452.52

general population (SMR=1.07) with cardiovascular management costs 10% lower; this minimized benefits and places this type of preventive strategy in doubt. Although the YLG are reduced to nearly half, the differential costs increase and the ICE is at least doubled compared to the baseline scenario; to obtain 1 YLG costs €7941 euros with A40, €12 221 with A40+E10, €5699 with A80, and €9978 with A80+E10.

In the most favorable scenario, in which patients with FH die at a rate 2.26 times that of the general population, the preventive strategies improved the gain in YLG over CP, reducing differential costs to around those of CP in some cases (€352 in the case of A80). The resulting ICE was €1241 for A40, €2589 for A40+E10, €319 for A80, and €1616 euros for A80+E10. In the analysis in which the discount rate for costs and results was the same at 6%, the results were not substantially changed. Figure 3 shows the outcome for the baseline scenario when applying different discount rates to the results.

Figure 3. Baseline scenario: cost-effectiveness values with an annual discount rate of 3% and 6% for YLG, and of 6% for costs.

DISCUSSION

To our knowledge, this is the first study involving patients with FH designed to determine the cost-effectiveness of a high dose statin (atorvastatin) either alone or in combination with other drugs. Substituting normal CP for patients with FH by a therapeutic strategy based on atorvastatin alone or in combination with ezetimibe would lead to a gain in health, although this would depend on the initial status of the patient and the previous treatment received. The gradation of the results, with higher values for the combined therapies and higher doses of atorvastatin, and the agreement between the different sensitivity analyses, show that any of the higher dose treatments are valid.

Compared with CP, the total costs of the treatments examined were always higher. This is because CP can involve patients receiving no preventive treatment or lower doses, and because survival (extra YLG) leads to further treatment costs. The costs of managing FH and cardiovascular events are inversely proportional to the effectiveness of treatment since this reduces the probability of these events (compared to CP, A80 offers the best results).

The ICE expresses the extra cost of obtaining 1 YLG more than with CP. According to their ICE values, the monotherapies and higher doses of atorvastatin appear to be the most efficient. Any of the treatments in any scenario is cost-effective in comparison with CP according to the threshold of efficiency usually taken into account -$20 000/YLG (€16 848/YLG at December 12, 2005)[28-30]; preventive treatment is therefore justified in all patients with a genetic diagnosis of FH. For those patients at highest cardiovascular risk, treatment should be adjusted to their needs and complemented with other therapies.

The model used is based on the different cardiovascular mortality shown by patients with FH, which conditions an SMR different to that of the general population. The reference model used (which came from a Dutch report)[5] is a new approach to the study of different mortality due to the effects of FH that, although it might be questioned in terms of its methodology and precision, provides an estimate with intervals of variability. The present model assumes that this different mortality may also be the case in other geographical areas with a similar population structure in which risk factors (mutations) are present. In addition, uncertainty is determined via a sensitivity analysis, approximating the mortality of patients with FH to that of the general population (the worst case scenario).

There is no evidence regarding how to extrapolate treatment effects to the end of life expectancy. This means that indirect data have to be used and several assumptions made. Given the different SMR compared to the general population, life tables allow estimates to be made regarding life expectancy, as well as the calculation of the PYLL owing to cardiovascular disease. After their calculation, the most plausible model is that which permits the effects of the different interventions on PYLL due to cardiovascular disease to be assessed.[2]

The presumption that a lifetime preventive treatment is worthwhile in genetic diseases manifested throughout life is logical, and is commonly made in economic models of statin use in cardiovascular disease.[28-31] Associated with more reservations is the presumption that the effect of treatment is maintained over life and that no-one abandons treatment or has it changed. The present model is static and simulates the hypothetical case that initial conditions persist during the expected lifetime, thus projecting the current health status forward. It is not a dynamic model that varies depending on interaction variables or intermediate results; the assumptions required would go far beyond the evidence available. Rather, its objective is to provide information regarding the

TABLE 7. **Years of Life Gained (YLG) and Costs of Treatment and Management of Cardiovascular Complications Associated With Each Preventive Treatment**

	YLG Compared to no Treatment						Cost of Treatment (Discount 6%)			Cost of Management (Discount 6%)			Total Cost (Discount 6%)		
	Worst Case Scenario		Baseline Scenario		Best Case Scenario		Worst Case Scenario	Baseline Scenario	Best Case Scenario	Worst Case Scenario	Baseline Scenario	Best Case Scenario	Worst Case Scenario	Baseline Scenario	Best Case Scenario
	Discount 3%	Discount 6%	Discount 3%	Discount 6%	Discount 3%	Discount 6%									
Normal treatment															
Total per patient	832.49	784.07	1737.89	1637.66	2635.67	2484.21	4688.122	4688.122	4688.122	12 571.969	20 605.397	30 929.613	17 260.091	25 293.519	35 617.735
Mean	0.94	0.89	1.97	1.86	2.99	2.82	5321	5321	5321	14 270	23 389	35 107	19 591	28 710	40 429
Standard deviation	0.51	0.48	0.99	0.92	1.44	1.35	4317	4317	4317	2677	7868	14,512	4712	8490	14 672
Atorvastatin 40 mg															
Total per patient	1108.38	1046.12	2281.68	2154.45	3417.99	3227.99	7256,558	7256.558	7256.558	12 194.403	19 674.984	29 331.901	19 450.961	26 931.542	36 588.459
Mean	1.26	1.19	2.59	2.45	3.88	3.66	8237	8237	8237	13 842	22 333	33 294	22 078	30 569	41 531
Standard deviation	0.32	0.29	0.51	0.47	0.67	0.61	1569	1569	1569	2473	7439	13 854	1568	6230	12 611
Atorvastatin 40 mg + ezetimibe 10 mg															
Total per patient	1509.12	1424.21	2978.71	2812.44	4321.51	4081.22	14 146.244	14 146.244	14 146.244	11 382.638	17 661.338	25 836.454	25 528.882	31 807.582	39 982.698
Mean	1.71	1.62	3.38	3.19	4.91	4.63	16 057	16 057	16 057	12 920	20 047	29 326	28 977	36 104	45 383
Standard deviation	0.42	0.38	0.62	0.55	0.76	0.68	3059	3059	3059	1941	6121	11 669	2148	4146	9396
Atorvastatin 80 mg															
Total per patient	1189.29	1122.46	2426.45	2291.12	3609.01	3408.38	7254.182	7254.182	7254.182	12 039.363	19 293.212	28 674.165	19 293.544	26 547.393	35 928.347
Mean	1.35	1.27	2.75	2.60	4.10	3.87	8234	8234	8234	13 666	21 899	32 547	21 900	30 133	40 781
Standard deviation	0.34	0.31	0.54	0.49	0.70	0.63	1569	1569	1569	2367	7184	13 437	1509	5983	12 197
Atorvastatin 80 mg + ezetimibe 10 mg															
Total per patient	1633.34	1541.40	3185.55	3007.68	4582.78	4327.94	14 143.867	14 143.867	14 143.867	11 107.371	16 970.104	24 621.066	25 251.238	31 113.971	38 764.933
Mean	1.85	1.75	3.62	3.41	5.20	4.91	16 054	16 054	16 054	12 608	19 262	27 947	28 662	35 317	44 001
Standard deviation	0.45	0.41	0.64	0.58	0.78	0.69	3.059	3059	3059	1777	5687	10 931	2277	3830	8708

differences that would result from using different treatment alternatives. Therefore, owing to the parsimony of the model, adverse events were not modeled. Idiosyncratic adverse events would have an equivalent effect on all arms of the model since CP treatment usually includes the use of statins (Table 1). Adverse events dependent on dosage would have a greater effect in the arms involving A80, approximating their results to those of the A40 arms under the efficiency threshold. In any event, the incidence of adverse events is reduced: 2.3% of patients experience an increase in liver enzyme levels (not related to inherent liver problems), 5 out of 100 000 person per year develop myopathy, and 1.6 in every 100 000 persons per year develop rhabdomyelosis.[32]

Approximating the cardiovascular risk via the use of the Framingham equations is an approach that has been used before in studies on FH.[33] The present model does not use the original equations but rather later versions that estimate the primary and secondary risk of an event. These were used for 2 reasons: *a)* a diagnosis of FH is very commonly established after an event at a young age; and *b)* there is a greater risk of a cardiovascular event among those patients who have already suffered one. In addition, people with FH are at high cardiovascular risk since they are born.[4] Therefore, it would be incorrect to estimate the risk of an event with formulae that apply to the general population (such as the REGICOR equation adapted for the Spanish population, or the SCORE equation). Even so, using these equations with age groups outside of those with which these equations were developed (30-55 years) can cause a bias in the results. They can be used with patients aged under 30 years since studies exist that show the relationship between hypercholesterolemia and ischemic cardiomyopathy in people under this age.[33] More questionable is their use with older people since the latter relationship is attenuated in the elderly.[33] In addition, there is no evidence of any effect of treatment for older people. However, the present

TABLE 8. Differential of Effectiveness Values (YLG), Differential Costs (Euros), and Incremental Effectiveness (Euros/YLG)

	Differential YLG						Differential Cost			Cost/YLG					
	Worst Case Scenario		Baseline Scenario		Best Case Scenario		Worst Case Scenario	Baselina Scenario	Best Case Scenario	Worst Case Scenario		Baseline Scenario		Best Care Scenario	
	Discount 3%	Discount 6%	Discount 3%	Discount 6%	Discount 3 %	Discount 6%				Discount 3%	Discount 6%	Discount 3%	Discount 6%	Discount 3%	Discount 6%
Atorvastatin 40 mg															
Total	275.90	262.05	543.79	516.79	782.32	743.78	2190.871	1638.023	970.724	7941	8361	3012	3170	1241	1305
Per patient	0.31	0.30	0.62	0.59	0.89	0.84	2487	1859	1102						
Atorvastatin 40 mg + ezetimibe 10 mg															
Total	676.63	640.13	1240.83	1174.78	1685.85	1597.01	8268.791	6514.063	4364.963	12 221	12 917	5250	5545	2589	2733
Per patient	0.77	0.73	1.41	1.33	1.91	1.81	9386	7394	4955						
Atorvastatin 80 mg															
Total	356.80	338.39	688.56	653.46	973.34	924.17	2033.454	1253.874	310.612	5699	6009	1821	1919	319	336
Per patient	0.40	0.38	0.78	0.74	1.10	1.05	2.308	1.423	353						
Atorvastatin 80 mg + ezetimibe 10 mg															
Total	800.86	757.32	1447.67	1370.02	1947.11	1843.73	7991.148	5820.452	3147.198	9978	10 552	4021	4248	1616	1707
Per patient	0.91	0.86	1.64	1.56	2.21	2.09	9071	6607	3572						

study uses the Framingham equations in an indirect manner, controlling other risk factors, in order to transform the proportional reduction in LDL-C into a relative reduction of cardiovascular risk and to be able to recalculate the PYLL. This methodology is applied equally in each arm of the intervention; there can therefore be no bias with respect to any particular intervention.

The first assumption was related to the study population: the cost per patient results from the imputation of the mean cost weighted by the prevalence of cardiovascular events, and the costs of the management of cardiovascular complications until the end of life expectancy. This assumption was made taking into account that the cost per patient is a valid central estimate of the situations that can arise with respect to the consumption of resources for the management of cardiovascular disease. The second assumption referred to the prevalence of lethal and non-lethal cardiovascular events, for which published values referring to the epidemiology of cardiovascular disease in Spain were used.[18,19] Their use implies that the only modifier with respect to time is the different probability of death as determined by age and sex since the proportional distribution of cardiovascular events is constant. The variation in incidence of cardiovascular events with respect to age and sex is therefore modulated. Their use also implies an equivalent proportional reduction in the incidence of any cardiovascular event due to treatment. At the end of the day, the limitation associated with these implications affects the consumption of resources and costs, but not effectiveness. This limitation was tested in the sensitivity analysis with scenarios in which the cost of management was 10% higher or lower than the central value.

Finally, the number and type of resources consumed per cardiovascular event was estimated using the criteria of experts. This, as well as being limited in terms of scientific evidence, implies the absence of variability in clinical practice and a smaller spread of costs. In addition, it implies a constant form of management over time for each type of event—which is rather improbable. The exploratory and informative nature of the model used, plus the fact that the assumptions made must translate into costs, justify these assumptions being made. The variability in clinical practice translated into management costs may be considered robust according to the sensitivity analysis. Finally, the consideration of the mean cost incorporates populational elements that confer a representative value on the cost for the Spanish national health system. This value can be extrapolated to other years and has a certain stability despite changes in management resources.

CONCLUSIONS

The results of this cost-effectiveness analysis show that the use of protocols based on atorvastatin at doses of 40 and 80 mg in patients with FH is associated with

a positive YLG result at a socially acceptable cost in comparison with normally accepted international thresholds. The greatest cost-effectiveness is achieved with atorvastatin 80 mg monotherapy. The addition of ezetimibe to treatment with atorvastatin 80 mg can provide additional positive effects for an acceptable increase in costs.

REFERENCES

1. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. Vol. II. New York: McGraw-Hill; 2001. p. 2863-913.
2. Alonso R, Castillo S, Civeira F, Puzo J, de la Cruz JJ, Pocoví M, et al. Heterozygous familial hypercholesterolemia in Spain. Description of 819 non related cases. Med Clin (Barc). 2002;118:487-92.
3. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat. 1992;1:445-66.
4. Scientific Steering Committee on behalf of the Simon Broome Register Group. The risk of fatal coronary heart disease in familial hypercholesterolemia. BMJ 1991;3030:893-6.
5. Sijbrands EJG, Westendorp RGJ, Defesche JC, De Meier PHEM, Smelt AHM, Kastelein JJP. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. BMJ. 2001;322:1019-23.
6. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised, placebo-controlled trial. Lancet. 2002;360:7-22.
7. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progresion of coronary atherosclerosis. JAMA. 2004;291:1071-80.
8. LaRosa JC, Grundy SM, Waters DD. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425-35.
9. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolemia: implications for clinical management. Atherosclerosis. 1999;142:105-12.
10. Smilde T, van Wissen S, Wollersheim H, Trip M, Kastelein J, Stalenhoef A. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet. 2001;357:577-81.
11. WHO Human Genetics Organization. Familial Hypercholesterolemia (FH), Report of a WHO Consultation: WHO/HGN/CONS/98.7. Geneva: World Health Organization; 1998.
12. OPS. Boletín Epidemiológico, Vol. 24 N.º 4, diciembre de 2003. La tabla de vida: una técnica para resumir la mortalidad y la sobrevivencia [cited Mar 2007]. Available from: http://www.paho.org/spanish/dd/ais/be_v24n4-tabla_vida.htm
13. Instituto Nacional de Estadística [cited Mar 2007]. Available from: http://www.ine.es
14. Discounting and mortality adjusting Years of Potential Life Lost (YPLL) [cited Mar 2007]. Available from: http://home.clara.net/sisa/paper6.htm
15. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H,Wilson PWF, et al. Primary and subsequent coronary risk appraisal: New results from the Framingham Study. Am Heart J. 2000;139: 272-81.
16. Civeira F. International Panel on Management of Familial Hypercholesterolemia Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis. 2004;173:55-68.
17. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. JAMA. 1996;276:1253-8.
18. Villar Álvarez F, Banegas Banegas JR, Donado Campos JM, Rodríguez-Artalejo F. Las enfermedades cardiovasculares y sus factores de riesgo en España: Hechos y cifras. Informe SEA 2003. Sociedad Española de Arteriosclerosis [cited Mar 2007]. Available from: www.searteriosclerosis.org
19. Medrano MJ, Boix R, Cerrato E, Ramírez M. Incidencia y prevalencia de cardiopatía isquémica y enfermedad cerebrovascular en España: revisión sistemática de la literatura. Rev Esp Salud Pública. 2006;80: 5-15.
20. Análisis y desarrollo de los GDR en el Sistema Nacional de Salud. Madrid: Ministerio de Sanidad y Consumo; 2000.
21. ORDEN 234/2005, de 23 de febrero, del Consejero de Sanidad y Consumo. Boletín Oficial de la Comunidad de Madrid. 2005;56:5-23.
22. Decreto Legislativo 1/2005, de 25 de febrero, del Consell de la Generalitat. Diario Oficial de la Comunidad Valenciana. 2005;22 Mar:4971 [cited 1 Oct 2006]. Available from: https:// www.docv.gva.es
23. Orden SLT/483/2005, de 15 de diciembre. DOGC. 2005;30 Dic;4540:43584.
24. Base de datos de costes sanitarios de SOIKOS, S.L. (1998).
25. Sociedad Española de Farmacéuticos de Atención Primaria. (SEFAP) Base de datos de medicamentos genéricos de SEFAP [cited 1 Oct 2006]. Available from: http://www.sefap.optyma.com
26. Base de datos de ventas de medicamentos de IMS correspondiente a los años 2000 a 2005 [comunicación interna].
27. Antoñanzas F. Hacia una homogeneización del valor de la tasa de descuento en los proyectos sociales. Libro de Comunicaciones de las XII Jornadas de Economía de la Salud. Madrid, 27-29 de mayo de 1992. Madrid: Comunidad de Madrid; 1993.
28. Franco OH, Peeters A, Looman CWN, Bonneux L. Cost effectiveness of statins in coronary heart disease. J Epidemiol Community Health. 2005;59:927-33.
29. McKenney JM, Kinosian B. Economic benefits of aggressive lipid lowering: a managed care perspective. Am J Manage Care. 1998;4: 65-74.
30. Tengs TO, Adams ME, Pliskin JS, Safran DG, Siegel JE, Weinstein MC, et al. Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal. 1995;15:369-90.
31. Franco OH, Steyerberg EW, Peeters A, Bonneux L. Effectiveness calculation in economic analysis: the case of statins for cardiovascular disease prevention. J Epidemiol Community Health. 2006;60: 839-45.
32. McKenney JM, Davidson MH, Jacobson TA, Guyton JR; National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006;97: C89-94.
33. Marang-van de Meen PJ, Ten Asbroek AHA, Bonneux L, Bonsel GJ, Klazinga NS. Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands. Eur Heart J. 2002;23:1922-30.