

ORIGINAL ARTICLE

Analysis of the budget impact for the Spanish National Health System of the fixed combination of amlodipine 5 or 10 mg and atorvastatin 10 mg

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Budget impact analysis;
Hypertension;
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Cardiovascular risk;
Health costs

Abstract

Objective: To carry out a Budget Impact Analysis (BIA) of the inclusion of the administration of the fixed combination (FC) of amlodipine 5 or 10 mg and atorvastatin 10 mg for approved indications in the Spanish National Health System (SNHS).

Material and methods: A BIA was carried out from the SNHS perspective for a 3-year period (2009-2011). A tree-type decision model was designed (patient tree), based on epidemiological data and scientific literature, in order to estimate the hypertensive population that could be treated with the FC. The total per annum BIA was calculated by attributing the retail price+VAT of the FC to the number of patients to be treated, and deducting the cost of the treatment for hypertension that was replaced and the updated average cost per patient of cardiovascular events (CVEs) prevented by the use of the FC by the SNHS during the period of study.

Results: The patient population likely to be treated with the FC was 51,104 patients (1st year), with a growth rate of 1%-2% over the following years, which means an annual cost (€) of 15.9 M (2009), 19.9 M (2010) and 24.1 M (2011), with a total of 60.0 M. The BIA was compensated showing negative impact values for the SNHS when the cost of replaced antihypertensive treatment and prevented CVEs was deducted, with savings of 69.9 M € over 3 years.

Conclusion: The BIA of a FC of atorvastatin and amlodipine shows that the use of this medication for approved indications could generate net savings for the SNHS of 9.9 M € for the period 2009-2011.

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PALABRAS CLAVE

Combinación fija
amlodipino/
atorvastatina;
Análisis de impacto
presupuestario;
Hipertensión;
Modelo económico;
Riesgo cardiovascular;
Costes sanitarios

Análisis del impacto presupuestario para el Sistema Nacional de Salud de la combinación fija de amlodipino 5 o 10 mg y atorvastatina 10 mg

Resumen

Objetivo: Realizar un análisis de impacto presupuestario (AIP) de la introducción en la prestación sanitaria del sistema nacional de salud (SNS) de la combinación fija (CF) de amlodipino 5 o 10 mg y atorvastatina 10 mg en la indicación aprobada.

Material y métodos: El AIP se ha realizado desde la perspectiva del SNS para un periodo de 3 años (2009-2011). Se ha diseñado un modelo de decisión tipo árbol (árbol de pacientes) construido a partir de datos epidemiológicos y la literatura científica para estimar la población hipertensa susceptible de tratamiento con la CF. El AIP, por año y en total, se ha calculado imputando el coste a PVP-IVA de la CF al número de pacientes por tratar, del que se sustrae el coste del tratamiento antihipertensivo que se sustituye y el coste por paciente promedio actualizado de los eventos cardiovasculares prevenidos para el SNS por el uso de la CF en el periodo de referencia.

Resultados: La población susceptible de tratamiento con la CF es de 51.104 pacientes (1.er año), con una tasa de crecimiento entre 1-2% en los sucesivos años, lo que supone un coste (€) anual de 15,9 M (2009), 19,9 M (2010) y 24,1 M (2011), totalizando 60,0 M. El AIP se ve compensado mostrando valores de impacto negativo para el SNS cuando se descuentan los costes del tratamiento antihipertensivo sustituido y eventos cardiovasculares prevenidos, mostrando un ahorro de 69,9 M € en 3 años.

Conclusión: El AIP de la CF de atorvastatina y amlodipino muestra que su uso en la indicación aprobada podría generar ahorros netos para el SNS en el periodo 2009-2011 de 9,9 M €.

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Introduction

The central goal of antihypertensive treatments is to reduce blood pressure to the appropriate values recommended by the leading scientific authorities.¹ However, clinical evidence has demonstrated that antihypertensive treatment alone only partially reduces the risk of cardiovascular events (CVE).² This observation is explained by the fact that complications related to hypertension, above all coronary disease and stroke, are usually due to multiple risk factors in addition to hypertension, such that only 14% of coronary events in hypertensive men and 5% in hypertensive women occur in the absence of additional risk factors.³⁻⁵ Major epidemiological studies carried out in Europe have established that dyslipidemia is the modifiable cardiovascular risk factor (CVRF) most commonly associated with hypertension.⁵⁻⁸ Various clinical studies have shown that a significant benefit can be obtained by administering statins at low doses in patients with multiple cardiovascular risk factors, including hypertension, and with cholesterol levels that are conventionally considered to be slightly elevated or even normal.⁷⁻⁹ Maintaining appropriate blood pressure and treatment with statins in patients with cardiovascular risk can reduce the incidence of heart attack and stroke by 70%.¹⁰

In the last 25 years, mortality due to cardiovascular diseases, primarily ischemic heart disease and cerebrovascular diseases, has constantly fallen, especially for cerebrovascular diseases.^{11,12} However, the evolution of hospital morbidity indicators,¹³ the analysis of tendencies by birth cohort,^{14,15} and the results of the REGICOR¹⁶ and MONICA¹⁷ incidence studies indicate that the reduced mortality is due more to

diminished lethality and improved survival than lower incidences, all of which implies an increased burden that cardiovascular disease has placed on health systems.

The Anglo-Scandinavian Cardiac Outcomes Trial included patients with arterial hypertension (AHT) and 3 or more cardiovascular risk factors.¹⁸⁻²⁰ The ASCOT study was designed to compare the effects of new antihypertensive therapies (amlodipine and perindopril when necessary) with the standard treatment (atenolol with diuretics if necessary) in reducing, as a primary objective, the number of fatal and non-fatal coronary events. In the lipid-lowering arm of the trial (LLA), patients with a total cholesterol less than 250 mg/dL, were randomised to receive 10 mg/day of atorvastatin or a placebo as well as the anti-hypertensive treatment.²¹ There was a significant reduction in the combined incidence of fatal and non-fatal heart attacks in the atorvastatin arm of the trial. It was for this reason that the independent safety committee of the ASCOT study decided to terminate the 5-year study after 3.3 years, in accordance with the previously specified criteria for the interim analysis of the LLA arm.²¹ No study until then had evaluated the benefit of statin treatment (atorvastatin at 10 mg) in a population such as that included in the LLA arm of the study: hypertensive patients in primary prevention, with moderate cardiovascular risk (3 or more CVRF), and with total cholesterol under 250 mg/dL.

The budget impact analysis (BIA) consists of a quantitative estimate of the changes predicted in the health costs for caring for a certain illness or group of patients when a new health care method is introduced for said illness/group of patients. For it to be used, it is important to be aware of

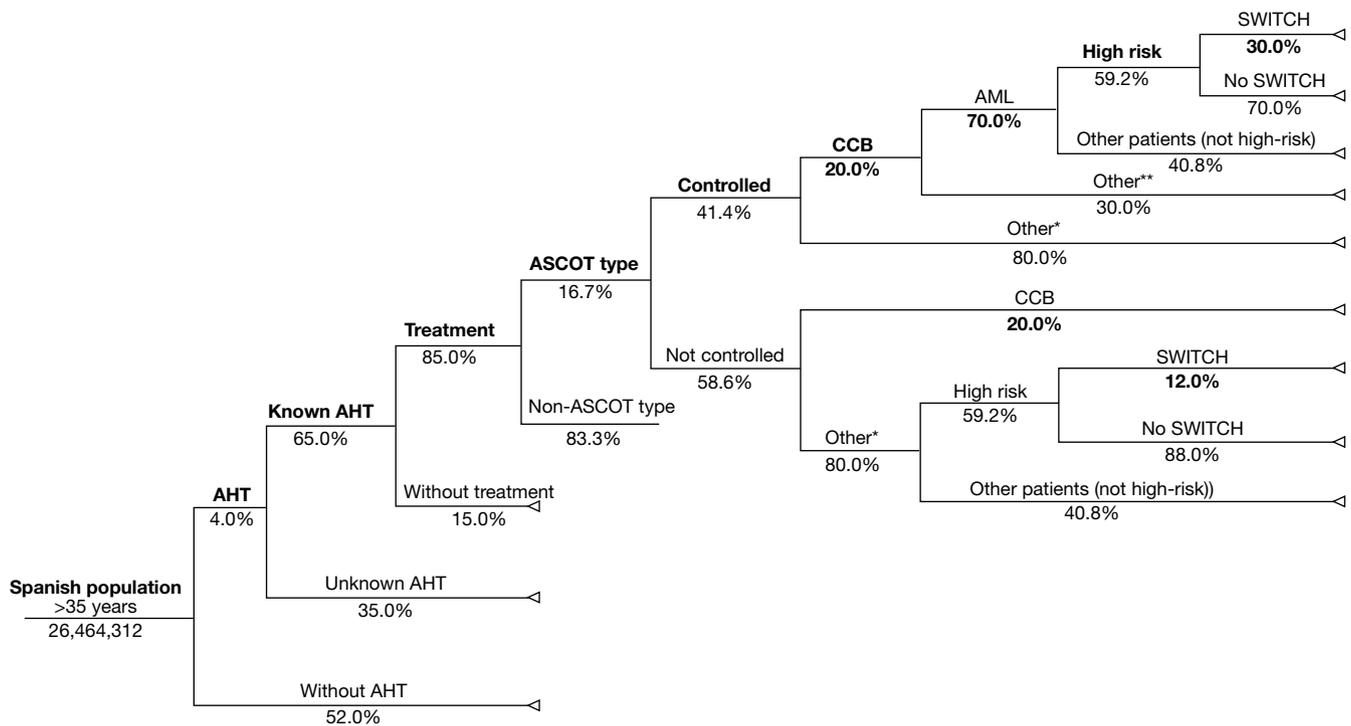
the number of patients likely to receive the new treatment, and assume a rate that is unknown *a priori* to introducing the treatment that allows us to quantify the economic impact of adopting the new health care method. The primary function of the BIA is to provide the decision maker with an estimate of the changes to health care costs caused by introducing the new procedure, taking into account the possible savings that would be produced in other facets of the health care system, such as morbidity, drug replacement, etc.^{22,23} This also allows for distinguishing the different impacts that a new procedure could have on various decision-makers (payers) related to the care given to patients with the illness treated by the new method. In our case, these would be those people contributing to the *sistema nacional de salud* (Spanish National Health System) (SNHS) for a national BIA, and the regions for the different partial BIA at regional level or for a decentralised SNHS

The objective of our study was to perform a BIA from the perspective of the SNHS, both as a single entity and as decentralised units, during the years 2009-2011 (with the corresponding sensitivity analysis in order to control for the associated level of uncertainty). We analysed the introduction of the fixed combination of 5/ 10 mg amlodipine + 10 mg atorvastatin for patients considered to have the indications approved in Spain: hypertensive patients with 3 or more concomitant CVRF, normal or slightly elevated cholesterol levels, and no clinical evidence of coronary disease.²⁴

Materials and methods

The BIA of the fixed combination (FC) of amlodipine+ atorvastatin was performed using an epidemiological decision model in the form of a decision tree that reflects the different populations of hypertensive patients along with their probabilities of occurrence, producing a patient tree (Fig. 1). The probabilities of the different branches of the tree are based on the demographic data for the current population and its projected growth in the next 3 years; the epidemiological data regarding the prevalence of arterial hypertension in Spain and its level of control, diagnosis and treatment, and data from epidemiological studies for characterising the population likely to receive the FC along with the rest of the variables necessary for constructing the model. The model was completed with data from market research and consultations with experts in the field in cases where assumptions had to be made without any available published data, particularly rates of introduction of the FC into the market. Once the population likely to be treated was defined, the cost of treatment was calculated for the 3-year projection, subtracting the costs for replacing amlodipine and the other antihypertensive treatments and the cost of the CVDs that would be prevented, all of which were obtained from the Spanish economic evaluation from the ASCOT-LLA study.²⁵

The data regarding the proportion of patients with controlled and uncontrolled blood pressure that would switch



AHT indicates arterial hypertension; AML, amlodipine; ASCOT, Anglo-Scandinavian-Cardiac-Outcomes-Trial; CCB, calcium channel blockers; SWITCH, chan high risk: hypertensive patients with diabetes and/or a metabolic disorder (PALPITATES Study, 77th EAS Congress 2008). *Other: Non-CCB antihypertensive treatment. **Other: antihypertensive treatment other than AML.

Figure 1 Patient tree with the probabilities of each branch, expressed as percentages, in the baseline scenario.

to the FC were obtained through a qualitative and quantitative investigation conducted by clinicians specialised in managing hypertension with over three years of experience, aged between 28-55 years, registered with the SNHS, and that had on some occasion prescribed amlodipine. In particular, we organised 2-hour meetings with 10 groups of primary care physicians (a total of 85 doctors), 2 groups of cardiologists (11), 4 groups of hypertension unit specialists (23), and 6 in-depth interviews (1 hour each) with 6 internal doctors. The meetings were held in Barcelona (4), Madrid (4), Seville (4), Valencia (2), and A Coruña (2), and the interviews were held in Seville (2), Valencia (2), and A Coruña (2). The summarised values were calculated in 2 waves or phases.

Study timeframe and perspectives

Since this project deals with a BIA, the perspective we chose to work from was that of the financier, in this case the SNHS,

both as a singular and decentralised entity, and so we have only included those health resources that are publicly financed. Therefore, we have not included the costs covered by the patient or the losses in occupational productivity and other indirect costs. The timeframe under consideration was 3 years, comprising 2009-2011.

Estimate of the patient population likely to receive the fixed combination of amlodipine and atorvastatin: baseline scenario

The baseline scenario for the BIA of the FC was elaborated using census information and projections for the Spanish population over 35-years-old by the *Instituto Nacional de Estadística* (National Statistics Institute) for the years 2009, 2010, and 2011 (Table 1).²⁶ From this global population, we extracted the populations corresponding to the weighted prevalence of AHT >35 years,²⁷ prevalence of

Table 1 Data on demographics, prevalence, and assumptions along with their sources of information, used in the Budget Impact Analysis of the fixed combination of amlodipine 5/10 mg and atorvastatin 10 mg in the baseline scenario

| Assumption | Year | | | Source |
|--|-------|-------|-------|---|
| | 2009 | 2010 | 2011 | |
| Growth of the Spanish population | – | 1.94% | 1.87% | INE, 2009 |
| Weighted prevalence of AHT in the Spanish population ≥35 years | 48.0% | 48.0% | 48.0% | Banegas. Hypertension. 2005;22:353-62 |
| Known prevalence of AHT | 65.0% | 65.0% | 65.0% | Banegas. Hypertension. 2005;22:353-62 |
| Prevalence of treated AHT | 85.0% | 85.0% | 85.0% | Banegas. Hypertension. 2005;22:353-62 |
| Prevalence of AHT without CD+3 or more CVRF and TC<250 mg/dL (ASCOT-LLA profile) | 16.7% | 16.7% | 16.7% | PALPITATES Study. 77th EAS Congress 2008 |
| Prevalence of hypertensives with controlled | 41.4% | 41.4% | 41.4% | PRESCAP Study 2006. Med Clin. BP 2008;130:681-7 |
| % of patients with controlled BP taking amlodipine that switch to the FC | 30.0% | 35.0% | 40.0% | Market research and expert opinions |
| % of patients with BP controlled with non-CCB treatment that switch to the FC | 0.0% | 0.0% | 0.0% | Market research and expert opinions |
| % of patients with uncontrolled BP not treated with CCB that switch to the FC | 12.0% | 15.0% | 18.0% | Market research and expert opinions |
| % of patients with uncontrolled BP treated with CCB that change to FC | 0.0% | 0.0% | 0.0% | Market research and expert opinions |
| Prevalence of hypertensives with diabetes and/or metabolic disorder (high risk) | 59.2% | 59.2% | 59.2% | PALPITATES Study. 77th EAS Congress 2008 |
| % of patients treated with non-CCB antihypertensive treatment | 80.0% | 80.0% | 80.0% | IMS (January 2009) |
| % of patients treated with amlodipine from among those receiving CCB | 70.0% | 70.0% | 70.0% | IMS (January 2009) |
| % of patients treated with 5 mg/day of amlodipine | 65.0% | 65.0% | 65.0% | IMS (January 2008) |
| 10 mg/day of amlodipine | 35.0% | 35.0% | 35.0% | |

AHT indicates arterial hypertension; ASCOT-LLA, Anglo-Scandinavian-Cardiac-Outcomes-Trial Lipid-Lowering Arm; BP, blood pressure; CCB, calcium channel blockers; CD, known coronary disease; CVRF, cardiovascular risk factor; FC, fixed combination of amlodipine 5/10 mg and atorvastatin 10 mg; INE, Instituto Nacional de Estadística; PALPITATES, Prevalence of ASCOT-LIKE patient: Integral Territorial Assessment to obtain epidemiological data in Spain; TC, total cholesterol.

known (diagnosed), treated, and controlled AHT,^{27,28} and with the profile corresponding to the hypertensive population from the ASCOT-LLA study¹⁸⁻²⁰ (hypertensives with 3 or more CVRF, without any known coronary disease and total plasma cholesterol levels <250 mg/dL), which were obtained from the PALPITATES⁹ study (Table 1), these being representative of the Spanish population. The baseline scenario was constructed upon this population after projecting the national prevalence of controlled and uncontrolled AHT,^{28,30} the proportion of patients in both subtypes that are receiving antihypertensive treatment with calcium channel blockers (CCB) and other drugs, and of them, the proportion and distribution of patients for each dosage of amlodipine (65% receiving 5 mg and 35% receiving 10 mg according to the 2008 IMS audit). We projected the prevalence in patients (both those controlled with amlodipine and those uncontrolled with non-CCB drugs) with the highest risk of suffering a cardiovascular event within the overall profile of ASCOT patients (those with a concomitant diagnosis of diabetes and/or a metabolic disorder [MD] according to NCEP-ATP III criteria),²⁹ and which experts would consider to be candidates for a switch from the previous antihypertensive treatment to the FC. Finally, we applied an expected percentage of patients that would change to the FC according to the expert criteria for each of the branches to be treated with the FC with different values according to the type of hypertensive patient (Fig. 1 and Table 1). Thus, the model considers two sources of patients likely to switch to the FC: a) high-risk hypertensive patients with a ASCOT-LLA type profile receiving amlodipine, in which a high rate of switching to the FC (at least 30%) would be expected, and b) high-risk hypertensive patients with an ASCOT-LLA type profile, uncontrolled and receiving non-CCB drugs, in which a low rate of switching to the FC (12%) would be expected.

It is assumed that the prevalence of AHT, the prevalence of hypertension treatment, the number of controlled patients, and those with an ASCOT-LLA type profile, are to be constant throughout the three years of the study, since no major variations in these values are expected in a 3-year period. However, in the baseline scenario, we included a progressive increase in the rates of switching to the FC in the two sources of patients during the second and third model years, which was 5% per year, in the case of patients that switch from amlodipine and 3% per year in the case of patients that switch from non-CCB drugs (Table 1).

Estimate of yearly treatment costs

The mean daily costs of the FC treatment were estimated using retail price and VAT established by the *Catálogo del Consejo General de Colegios Farmacéuticos de España*³¹ (Catalogue of the Spanish Pharmaceutical Colleges General Council), which came to €26.44 for the Duet[®] 5/ 10 and €34.00 for Caduet[®] 10/ 10. For amlodipine, we used the currently approved reference prices (for 2009), which are €8.08 (5 mg) and €16.17 (10 mg). The annual treatment cost for the FC was calculated by multiplying the retail price and VAT, weighted according to the proportion of use of the available dosages, by the level of compliance (number of days that the patient effectively takes the treatment) in

one year. We determined that the best estimate of treatment compliance, at least from the point of view of costs, is the intensity of medication use as measured by the proportion of days in one year covered by the prescriptions filed by the patient in the pharmacy. The best estimate found was 82.4%, which corresponds to 301 days of effective treatment per year.³² For 2010 and 2011, we considered the same scenario of treatment compliance. According to the IMS audit, the patients will consume the FC in proportions of 5/ 10 mg in 65% of cases, and 10/ 10mg in 35% of cases, respectively. We assumed that this proportion to remain constant during the analysis period (Table 1). The cost computed by this method corresponds to the pharmaceutical costs of using the FC.

Once the pharmaceutical costs of the introduction of the FC were calculated for the SNHS, the pharmaceutical costs of the treatments that are substituted by the FC as well as the potential costs from the prevented CVE⁷ during the 3-year period must be discounted. The annual cost of the replaced treatments is made up of two components: the cost of amlodipine (reference price), in the case of patients taking amlodipine that switch to the FC (an estimated 30% in the baseline scenario, Fig. 1, switch patients), and the average cost of antihypertensive drugs in the case of uncontrolled patients taking non-calcium antagonists that switch to the FC (an estimated 12% in the baseline scenario, Fig. 1 and Table 1), and that are considered to be new FC patients. The mean cost of antihypertensive drugs per day of treatment was obtained by dividing the annual cost of antihypertensive treatment in 2008 by the total estimated number of hypertensive patients at the beginning of 2009 according to the patient tree. The annual cost of antihypertensive treatment was obtained by projecting the accumulated rate of pharmaceutical expenses from the year 2001 until now (according to the *Ministerio de Sanidad y Política Social* [Ministry of Health and Social Policy]) from the annual cost of antihypertensive treatment calculated in 2001 by García del Pozo et al.³³ The estimated cost of treatment per day was €0.753 in 2008 for the baseline scenario.

The costs of prevented CVEs were derived from the costs avoided in direct health resources left unused by employing the FC and quantified using the results from the ASCOT study and an economic evaluation of costs in Spain that was performed afterwards.²⁵ According to this evaluation, the mean savings per patient, once updated for accumulated inflation, was €524 in 3 years. This value was multiplied by the estimated number of patients that would be treated with the FC, assuming that the costs avoided by preventing CV events in the 1st year is 15% 50% in the 2nd year, and 100% in the 3rd year. This estimate was based on the results of the ASCOT study, in which a clinical benefit was already observed in the prevention of cardiovascular events 90 days after the study had commenced.⁷ Therefore, the patients that start FC treatment during the 1st year benefit 100% from the prevented cardiovascular events, distributing the avoided costs by 15% in the 1st year, 35% in the 2nd year, and the remaining 50% in the 3rd year. However, the patients that enter the BIA model during the 2nd year only benefit from 50% of the avoided costs (again, 15% in the 1st year and 35% in the 2nd year). Finally, the patients that enter in the 3rd year only benefit from 15%

Sensitivity analysis

Given that any economic model carries with it some level of uncertainty due to the assumptions made, we performed a threshold-type univariate sensitivity analysis with those variables that were estimated to have an associated uncertainty, using values for the baseline scenario within the range of variation that would be plausible in normal clinical practice. For this, the following assumptions were analysed within the range that varied between ± 50 and $\pm 25\%$ according to the variable, over the value used in the baseline scenario. The different assumptions were: the cost of amlodipine treatment, the market share percentage distribution of the FC treatments, the percentage of high-risk patients, the percentage of ASCOT-type patients, the percentage of patients receiving treatment with amlodipine and calcium antagonists, the percentage of high-risk ASCOT-type patients with controlled AHT treated with amlodipine that would make the switch to the FC, and high-risk ASCOT-type patients with uncontrolled AHT, and with non-calcium antagonist treatment that switch to the FC. Similarly, we included variants of the parameters such as the percentage of high-risk patients, which was modified by the diabetic patients and those that only suffered an MD. The results from these sensitivity analyses are presented in a tornado graph (Fig. 2).

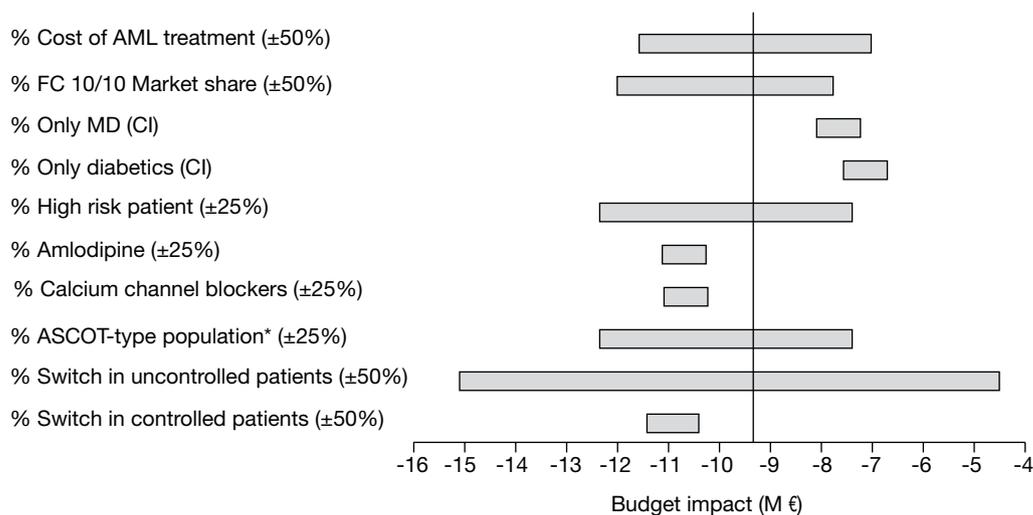
Furthermore, we performed univariate threshold analyses in order to find the cut-off point that would produce a change in the BIA value (incremental costs or savings) with the mean cost/day variables for a non-calcium antagonist antihypertensive treatment, number of days of treatment compliance per year, 3-year cost of prevented CVE, and the proportion of monotherapy with the FC in patients that change to a non-calcium antagonist antihypertensive treatment.

Results

Figure 1 shows the estimated populations that would be treated with the FC according to the patient tree model developed for the BIA. Using 2009 census data, and the estimated prevalence of arterial hypertension, treated AHT, controlled disease, etc., and the proportion of patients that switch to the FC, the model predicted that a total of 51,104 patients would be treated using the FC in Spain in the 1st year (2009), which would increase to 64,095 in the 2nd year and 77,520 in the 3rd year (Table 2). Starting with the assumption that the percentage distribution of the two different commercialised FC treatments are 65% (5/10 mg) and 35% (10/10 mg), a total of 33,218 patients would be treated with the 5/10 mg FC and 17,887 with the 10/10 mg FC in the 1st year, which would constitute a national pharmaceutical cost of €15,913,127 in 2009, €19,958,123 in 2010, and €24,138,639 in 2011 (Table 3). The global budget impact in these three years, taking into account only the costs of acquiring the new FC, would be €60,009,889.

From this global impact, the cost of treatment that was replaced by the FC was discounted, constituting a savings of €10,171,968 in the 1st year, €12,849,169 in the 2nd year, and €15,616,429 in the 3rd year, totalling €38,637,566 during the 3-year period (Table 3). Furthermore, given the expected effect of the FC on reducing expected CVEs (prevented events), we computed the costs avoided in the treatment for these prevented events as savings, constituting €4,016,808 in the 1st year, €10,393,594 in the 2nd year, and €16,827,042 in the 3rd year. By combining these two types of avoided costs, a total of €69,875,011 was calculated in savings during the 3-year period (Table 3).

Finally, the net impact of the introduction of the FC, once the avoided costs were discounted, was +€1,724,351 in the 1st year (2009), €-3,284,640 € in the 2nd year (2010), and



AML indicates amlodipine; ASCOT, Anglo-Scandinavian-Cardiac-Outcomes-Trial; CI, confidence interval; FC, fixed combination. *We have estimated that the high-risk group corresponds to 59.2% of ASCOT-type patients, also having a metabolic disorder (MD) and/or diabetes; Switch: treatment change.

Figure 2 Tornado graph showing the results of the univariate sensitivity analysis for several variables with a level of uncertainty in the budget impact analysis of the fixed combination of amlodipine 5/10 mg and atorvastatin 10 mg.

Table 2 Estimate of the number of patients likely to receive treatment with the fixed combination of amlodipine 5/10 mg and atorvastatin 10 mg in the baseline scenario*

| | Year 2009 | 2010 | 2011 |
|---|---------------|---------------|---------------|
| Population >35 years according to census data | 26,464,312 | 26,977,717 | 27,483,506 |
| Population with AHT | 12,702,870 | 12,949,304 | 13,192,083 |
| Population with known AHT | 8,256,865 | 8,417,048 | 8,574,854 |
| Population with AHT receiving pharmacological treatment | 7,018,336 | 7,154,491 | 7,288,623 |
| ASCOT-type population ^a | 1,172,194 | 1,194,934 | 1,217,337 |
| ASCOT-type population with controlled BP ^b | 485,288 | 494,703 | 503,978 |
| Population taking CCB drugs | 97,058 | 98,941 | 100,796 |
| Population taking amlodipine | 67,941 | 69,259 | 70,557 |
| Population taking amlodipine with a high risk of CVE ^c | 40,221 | 41,001 | 41,770 |
| Population that switches from amlodipine 5 to FC 5/10 | 7,843 | 9,328 | 10,860 |
| Population that switches from amlodipine 10 to FC 10/10 | 4,223 | 5,023 | 5,848 |
| Total population that switches from amlodipine to FC | 12,066 | 14,350 | 16,708 |
| ASCOT-type population with uncontrolled BP ^b | 686,906 | 700,231 | 767,359 |
| Population NOT taking non-CCB | 549,525 | 560,185 | 613,887 |
| Population NOT controlled with non-CCB at high risk of CVE ^c | 325,319 | 331,630 | 363,421 |
| Population that switches from a non-CCB drug to FC 5/10 | 25,375 | 32,334 | 39,528 |
| Population that switches from a non-CCB drug to FC 10/10 | 13,663 | 17,411 | 21,284 |
| Total population changing to the FC (new patients) | 39,038 | 49,744 | 60,812 |
| <i>Total number of patients estimated to be treated with the FC</i> | <i>51,104</i> | <i>64,095</i> | <i>77,520</i> |
| With FC 5/10 | 33,218 | 41,662 | 50,388 |
| With FC 10/10 | 17,887 | 22,433 | 27,132 |

AHT indicates arterial hypertension; ASCOT, Anglo-Scandinavian-Cardiac-Outcomes-Trial; BP, blood pressure; CCB, calcium channel blockers; CVE, cardiovascular event; FC, fixed combination.

*The values for prevalence and percentages used in the different steps of the model can be seen in Figure 1 and Table 1.

^aASCOT-type population: hypertensive patients (BP \geq 140/90), without any known coronary disease, total cholesterol <250 mg/dL, and 3 cardiovascular risk factors.

^bControlled BP: BP <140/90; Uncontrolled BP: BP >140/90.

^cHigh risk: patients with type I or II diabetes and/or metabolic disorder.

€-8,304,833 in the 3rd year (2011) of treatment. At the end of the three-year period, the net global budget impact was €-9,865,121 (Table 3).

Taking into account the population older than 35 years, all of the data and previously mentioned assumptions, and the different calculations performed by all of the regions, we deduced that the BIA would produce a net negative result in all of them; i.e. savings would be made with the introduction of the FC (Table 4). The regions that would most benefit in savings would be Andalusia (€-1,649,489) Catalonia (€-1,579,199), and Madrid (€-1,326,545), Table 4.

Sensitivity analysis

The sensitivity analyses that we performed (Figs. 2-5) show that the BIA estimated for the study period of 2009-2011 is very robust, since the net result is very similar in the different scenarios, and remains negative in most of the new scenarios. As such, for any distribution of the 5/10 and 10/10 FC presentations, cost/day of amlodipine treatment, prevalence of ASCOT-type and high-risk patients (including

diabetics and MD patients) that switch to the FC, the percentage of patients that change from amlodipine or a non-calcium antagonist treatment, and the percentage of patients treated with amlodipine or a calcium antagonist, the BIA result is always negative, generating savings for the SNHS, whether taken as a centralised or decentralised entity (Tornado Graph, Fig.2).

In addition, the threshold-type univariate sensitivity analyses show that the BIA will always be negative (a net production of savings for the SNHS) independent of the number of days per year in which the patients take the FC. At the same time, the BIA would be sensitive to the variations in cost/day of non-calcium antagonist antihypertensive treatments, the percentage of patients that use the FC as a monotherapy when changing from a non-calcium antagonist treatment, and when the mean cost/patient of prevented CVE changes (Figs. 3-5). In this respect, the 3-year BIA would be positive (a net additional cost for the SNHS) if the cost/day of non-calcium antagonist antihypertensive treatments were to fall below €0.54/day, the percent of FC monotherapy treatments were to fall below 72% of patients that switch

Table 3 Estimate of the annual costs (€) of treatment with the fixed combination of amlodipine 5/10 mg and atorvastatin 10 mg in the baseline scenario derived from the estimates of the treated population

| | Year | | | 3-year BIA ^a |
|--|------------------|-------------------|-------------------|-------------------------|
| | 2009 | 2010 | 2011 | |
| Costs of patients treated with FC 5/10 | 9,398,667 | 11,787,736 | 14,256,847 | |
| Costs of patients treated with FC 10/10 | 6,514,460 | 8,170,387 | 9,881,792 | |
| Annual cost | 15,913,127 | 19,958,123 | 24,138,639 | 60,009,889 |
| Costs avoided by replacing the amlodipine treatment ^b | 1,323,838 | 1,574,440 | 1,833,095 | 4,731,374 |
| Costs avoided by replacing the non-CCB treatment ^c | 8,848,130 | 11,274,728 | 13,783,334 | 33,906,192 |
| Total costs avoided by treatment replacement | 10,171,968 | 12,849,169 | 15,616,429 | 38,637,566 |
| Costs avoided by preventing CVE during 3 years ^d | 4,016,808 | 10,393,594 | 16,827,042 | 31,237,445 |
| Total costs avoided | 14,188,776 | 23,242,763 | 32,443,472 | 69,875,011 |
| <i>Net result (annual cost-costs avoided)</i> | <i>1,724,351</i> | <i>-3,284,640</i> | <i>-8,304,833</i> | <i>-9,865,121</i> |

CCB, calcium channel blockers; CVE, cardiovascular event; FC, fixed combination.

^aBIA: budget impact analysis assuming an average of 301 treatment days per year.

^bCalculated with reference prices for amlodipine in 2009.

^cCalculated as a mean cost per day of €0.753 using reference 31.

^dUpdated cost of CVE in 3 years without pharmacological treatment, estimated at €524 according to reference 24 and weighted annually according to reference 7 (see explanation of the calculation in the text).

from a non-calcium antagonist antihypertensive treatment, or the mean cost/patient of the prevented CVE were to fall below €361 per event. However, in each of the mentioned turning point values that change the net result of the BIA from negative to positive in the 3-year period, the last year of the BIA still shows a savings for the SNHS, although these savings would not be sufficient to compensate for the costs incurred during the first two years. These values would have to be lowered to €0.29/day (39%), and €265, respectively, in order for the BIA to no longer result in savings in the 3rd year of the model (Figs. 3-5).

Discussion

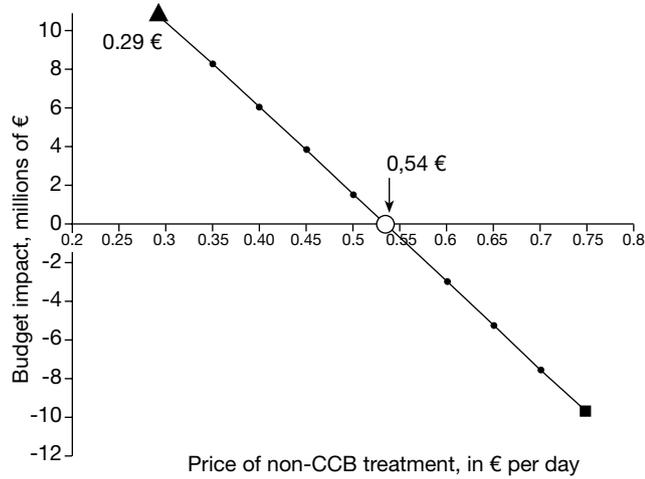
The BIA model presented by this study estimated that the total possible number of patients to be treated with the FC in the 1st year of analysis (2009) would be 51,104, increasing to 64,095 in the 2nd year and 77,520 in the 3rd year for all of Spain. This estimate appears reasonable when taking into account the fluctuations in the antihypertensive treatment market in the Spanish health system and in other countries similar to ours, the recommendations given by clinical guides,³³⁻³⁵ and the logical resistance of physicians to rapidly incorporate new therapeutic innovations.

The net result of the introduction of the FC shows relevant savings for the SNHS during the 3-year study period, with a growing tendency in the savings produced as the timeline progresses in the analysis, and in particular, when the number of patients that switch to the FC of amlodipine and atorvastatin from their current treatments increases. This last result could be explained in light of the ASCOT-LLA study^{7,18-21} by the greater number of CVEs prevented by increasing the use of the FC. However, the limitation of a singular 3-year projection limits our analysis in that we cannot observe the complete savings that would be derived from the CVE prevented in patients that start treatment during the 2nd or 3rd years of the BIA. For this reason, the

Table 4 Budget impact analysis during the 2009-2011 by region

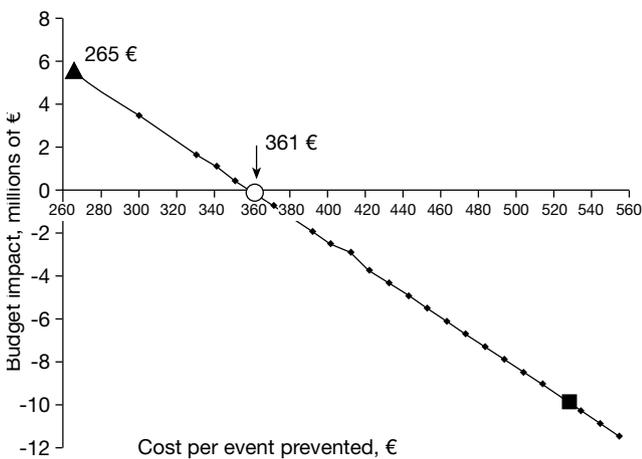
| Region | Budget impact in 3 years (millions of €) | | |
|-----------------------|--|---------------|-------------|
| | FC treatment cost | Avoided costs | Net results |
| Andalusia | 10,074,762 | -11,724,248 | -1,649,486 |
| Aragon | 1,815,535 | -2,115,279 | -299,744 |
| Asturias | 1,560,779 | -1,820,092 | -259,313 |
| Balearic Islands | 1,351,876 | -1,571,899 | -220,023 |
| The Basque Country | 3,034,135 | -3,538,329 | -504,195 |
| Canary Islands | 2,613,508 | -3,038,687 | -425,179 |
| Cantabria | 798,526 | -929,995 | -131,469 |
| Castile-La Mancha | 2,623,861 | -3,051,631 | -427,770 |
| Castile-Leon | 3,586,316 | -4,181,112 | -594,796 |
| Catalonia | 9,562,288 | -11,141,486 | -1,579,199 |
| Ceuta | 83,444 | -97,247 | -13,803 |
| Extremadura | 1,413,892 | -1,648,085 | -234,193 |
| Galicia | 3,869,139 | -4,510,951 | -641,813 |
| Madrid | 8,080,582 | -9,407,126 | -1,326,545 |
| Melilla | 74,565 | -87,121 | -12,557 |
| Murcia | 1,728,670 | -2,009,481 | -280,812 |
| Navarre | 828,195 | -964,522 | -136,326 |
| Rioja | 425,815 | -495,926 | -70,111 |
| Valencia | 6,484,000 | -7,541,783 | -1,057,783 |
| FC, fixed combination | | | |

first year that the FC was introduced results in an economic balance that would have to be paid by the SNHS. However, the result of the costs and savings produced during the second year of treatment are compensated and even



ECCB indicates calcium channel blockers.
 ■ Baseline scenario; ○ point of inflexion in which the BIA results in no net savings during the 3-year period; ▲ point at which the BIA shows no savings in any of the 3 years.

Figure 3 Threshold-type univariate sensitivity analysis of the mean cost/day of antihypertensive treatment when switching from a non-calcium channel blocker (CCB) to the fixed combination of amlodipine 5/ 10 mg and atorvastatin 10 mg.

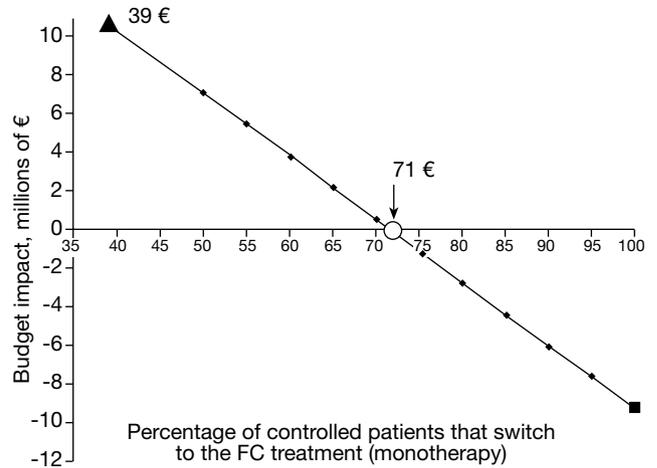


■ Baseline scenario; ○ point of inflexion in which the BIA results in no net savings during the 3-year period; ▲ point at which the BIA shows no savings in any of the 3 years.

Figure 4 Threshold-type univariate sensitivity analysis of the mean cost per patient of a cardiovascular event that was prevented during the 3 years when the treatment was changed to the fixed combination of amlodipine 5/ 10 mg and atorvastatin 10 mg.

surpassed by the small economic savings that clearly increase from the third year onwards, constituting a net national savings of €9.9m in the baseline scenario. These results were observed for the SNHS whether as a centralised or decentralised entity.

Given that the health information system is not perfect, the results obtained from this BIA are not free from a particular level of uncertainty in the projections and estimates performed. In this respect, we have been able to minimise the possible errors and increase the certainty of the



■ Baseline scenario; ○ point of inflexion in which the BIA results in no net savings during the 3-year period; ▲ point at which the BIA shows no savings in any of the 3 years.

Figure 5 Threshold-type univariate sensitivity analysis of the percentage of patients treated with the fixed combination of amlodipine 5/ 10 mg and atorvastatin 10 mg as a monotherapy when changing from a non-calcium antagonist antihypertensive treatment. FC indicates fixed combination.

estimates that we have made due to the sensitivity analysis conducted (including over 14 parameters, although we used a univariate methodology). This analysis has allowed us to prove the robustness of the BIA when modifying the different variables that are subject to uncertainty, including the cost of acquiring amlodipine and the number of days in which the patients effectively take the treatment, resulting in savings in all cases. Only the cost/patient of the prevented CVE, the percentage of patients that replace a non-calcium antagonist antihypertensive treatment with the FC, and the mean cost per day of antihypertensive treatment have proven to be sensitive in this analysis, presenting inflexion points in which the BIA shows no net savings with the sum of the 3 study years (although savings are observed from the 3rd year onwards in the BIA) or show no savings in any of the study years, as observed in our figures.

To this respect we must firstly point out that the present BIA is conservative, as it does not impute the complete monetary benefits derived from the prevention of cardiovascular events in the patients that start treatment during the 2nd or 3rd years of the study, it does not include any co-pays on the part of the patients receiving the FC treatment, it has overestimated the number of days of effective compliance with the FC treatment as being more than the 82% of possible treatment days when the scientific literature places it below 70%³⁶⁻³⁸ and it did not compute increases in work productivity derived from reducing the occupational losses attributable to those patients in which a CVE was prevented. In addition, we must point out that the plausibility of reaching the inflexion points is low. As such, a reduction in the cost/day of non-calcium antagonist antihypertensive treatments would be below €0.54/day, the point at which the BIA shows no savings during the 3 years (although savings are observed after the 3rd year). This seems very unlikely in the current health care environment given

the tendencies for pharmaceutical spending on antihypertensive treatment.³³ Similarly, it appears to be highly improbable that the mean cost/day could be reduced below €0.29/day, which is the point below which no savings would be produced in any year for the SNHS. A similar deduction can be made for the percentage of patients using the FC as a monotherapy after switching from a non-calcium antagonist treatment. The percentage of patients that add the FC to their existing antihypertensive treatment would have to be greater than 28% in order for the global BIA to show no savings (although they would appear after the third year) or greater than 61% for no savings to be seen in any of the model years. This seems highly improbable if we take into account the recently performed PRESCOT²⁸ study carried out in Spain in the field of primary care, in which 59% of the almost 12,000 hypertensive patients were receiving antihypertensive treatment as a monotherapy. Finally, it also seems implausible that the cost/patient of the prevented CVEs could be reduced below €361 per event, at which point the BIA would yield a net loss, if the current protocols for the clinical management of CVE patients remains the same.³⁹ To this end, we must point out that the risk of suffering a CVE, even in the Spanish population, could be very different from that of the original ASCOT study (Norwegian and Scottish) when the population has the same CVRF as that of the clinical trial, precisely the type of patient that would benefit from the use of the FC of amlodipine and atorvastatin.⁴⁰

We have not found any other similar studies that analyse a BIA with other fixed combinations of lipid-lowering drugs, and therefore, no direct comparisons can be made. However, the CARPE study, which researched the use of a fixed combination in a single dosage of amlodipine and atorvastatin as a strategy for improving compliance with treatment in patients with multiple cardiovascular risk factors, demonstrated the effectiveness of this combination in treating the two main risk factors for cardiovascular diseases.³⁷ In addition, the FC of amlodipine and atorvastatin appear to translate into an improvement in patient compliance with treatment, at least during the first year, although these rates are still below those used in our BIA model.^{36,38}

Model limitations

This BIA model, as in all models, has limitations. The first and foremost is that it is a model for projecting the use of a medication in the future, based on some assumptions and the expected attitude of attending clinicians when faced with the introduction of a new FC in the slew of therapeutic options, whose indication recommends the use of a drug for conditions in which it normally is not prescribed, such as in patients with normal cholesterol levels. This could make the true percentages of switching or using the FC vary greatly in real life. However, in spite of this precaution, the sensitivity analysis has shown that the results are not sensitive to this variable, showing increased savings as the number of patients being treated with the FC increases.

In second place, we have pointed out that the model was not able to estimate the level of co-pay expected from the patients that would receive treatment with the FC, which would positively impact the budgets of the SNHS if they had been taken into account. Nor were we able to estimate the

positive economic impact of the increases in work productivity (in terms of the patients) due to the reduced occupational losses attributable to those patients in which a CVE is prevented. The rest of the possible limitations that arise from making assumptions, including the discount rate, have been managed using the sensitivity analysis, treating each parameter separately in order to improve the evaluation of the changes observed.

Conclusions

Even in spite of the aforementioned limitations, the BIA of the FC of amlodipine 5/10 mg and atorvastatin 10 mg when used under the appropriate indications could generate net annual savings of €9.9 m for the SNHS during a period of 3 years. These savings, observed proportionally in each region, could be multiplied if the time period of the model was expanded or a greater number of patients were to receive the combination.

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Conflict of interest

Javier Rejas and Belén Ferro are employees of Pfizer España. Marina De Salas works for TFS, a consultant company employed by Pfizer. Jaime Fernández de Bobadilla has no conflict of interest.

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