

Use of Antihypertensive Drugs in Spain (1995-2001)

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Objectives. In the last few years there have been changes in the pattern of consumption of antihypertensive drugs in Spain. This study aimed to describe the pattern of use in Spain from 1995 to 2001, its compliance with guidelines, and its economic impact. An aim of particular interest for our study was the impact of angiotensin II receptor antagonists on the consumption of the drugs from other therapeutic subgroups.

Patients and method. Information on drug utilization was obtained from the ECOM database of the Spanish Ministry of Health, which records the number of packages charged to the National Health System. Data were expressed in defined daily dose (DDD) and DDD per 1000 inhabitants per day (DDD/1000).

Results. Antihypertensive consumption in Spain increased from 113.1 DDD/1000 in 1995 to 182.8 in 2001 (an increase of 61.65%). In 2001, angiotensin II receptor antagonists accounted for 25% of the costs and 14% of the consumption. Overall, costs increased from 646.42 million euros in 1995 to 1144.77 million euros in 2001.

Conclusions. The consumption of antihypertensive drugs in Spain has increased remarkably in the last 7 years. Likewise, costs have increased proportionately, although the contributions of different therapeutic subgroups have been unequal. The impact of angiotensin II receptor antagonists has been considerable, both on consumption and on costs.

Key words: Hypertension. Antihypertensives. Consumption. Costs. Drug utilization.

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Utilización de antihipertensivos en España (1995-2001)

Introducción y objetivos. En los últimos años se han producido cambios en el patrón de utilización de los antihipertensivos en España. Describir este patrón de utilización entre 1995 y 2001, su adecuación a las recomendaciones y sus repercusiones económicas ha sido el objetivo del presente trabajo. Se ha dedicado particular atención al impacto que la introducción de los antagonistas de los receptores de la angiotensina II ha podido tener en el consumo de otros subgrupos.

Pacientes y método. La información sobre el consumo de antihipertensivos en España se obtuvo de la base ECOM del Ministerio de Sanidad y Consumo, que contiene las especialidades farmacéuticas facturadas con cargo al Sistema Nacional de Salud en el ámbito extrahospitalario. El consumo se expresó en dosis diarias definidas (DDD) por 1.000 habitantes y día (DHD).

Resultados. El consumo de antihipertensivos en España pasó de 113,1 DHD en 1995 a 182,8 DHD en 2001 (un 61,6% de incremento). Para el año 2001, los antagonistas de receptores de la angiotensina II supusieron casi el 25% de los costes, frente a un 14% del consumo. Para el conjunto de los antihipertensivos, los costes han pasado de 646,42 millones de euros en 1995 a 1.144,77 en 2001.

Conclusiones. El consumo de antihipertensivos en España se ha incrementando de un modo notable en los últimos 7 años. El coste global se ha incrementado de forma proporcional, aunque la contribución de los diferentes subgrupos es muy desigual. El impacto de la introducción de los antagonistas de receptores de la angiotensina II ha sido muy importante, tanto en el consumo como en el coste.

Palabras clave: Hipertensión. Antihypertensivos. Consumo. Coste. Utilización de medicamentos.

INTRODUCTION

Hypertension is currently considered a major public health problem because of its importance as a cardiovascular risk factor. The recent World Health Report 2002 of the World Health Organization (WHO) states that high blood pressure is the primary or

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ABBREVIATIONS

ACE inhibitors: angiotensin-converting enzyme inhibitors.
 ARBs: angiotensin II receptor blockers (angiotensin II antagonists).
 ATC: Anatomical Therapeutic Chemical class of medications.
 BBs: beta-blockers.
 CCBs: calcium channel blockers.
 DDD: defined daily doses.
 DDD/1000: defined daily doses per 1000 inhabitants and day.
 JNC VI: Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
 JNC VII: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
 WHO: World Health Organization.
 WHO-ISH: World Health Organization-International Society of Hypertension.

secondary cause of 50% of all cardiovascular diseases worldwide.¹ In Spain, 1 out of every 4 deaths and 1 out of every 2.5 deaths caused by cardiovascular disease is related to high blood pressure.²

The last few years have witnessed considerable changes in the treatment of high blood pressure in Spain. Between 1985 and 1995, the use of antihypertensive agents tripled and resulted in an eight-fold increase in the pharmaceutical expenditure for these agents. The pattern of antihypertensive drug consumption during this period changed substantially, although it still did not adhere to the available scientific criteria. In 1995 thiazide diuretics and beta-blockers (BBs) accounted for no more than 30% of all consumption, whereas angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium channel blockers (CCBs) represented more than 60%.³ During the second half of the 1990s, angiotensin II receptor blockers (ARBs) were introduced to the Spanish market, expanding the options regarding antihypertensive agents. These new active ingredients are expensive drugs that enhance the high costs of these therapies. According to data from the Sistema Nacional de Salud (National Health Service), in 2001 a total of 78 114 million pesetas were spent on hypotensive agents that act on the renin-angiotensin system (ACE inhibitors and ARBs), and 45 990 million pesetas were spent on CCBs. When the costs of these two subgroups are combined with the costs of all other antihypertensives, these drugs account for 15% of all pharmaceutical costs.⁴

An understanding of the trends in the consumption

of the available drugs in public and private healthcare, and the costs for antihypertensive therapies in Spain in recent years was the main objective of this study. Other objectives were to describe the impact of ARBs on the consumption of other drug subgroups and trends in the cost per day of the various antihypertensive agents.

PATIENTS AND METHODS

In order to evaluate the antihypertensive drugs available in Spain, information was compiled for the subgroups and years being studied on the number of active ingredients and fixed-dose combinations, the medications and commercial packages listed in the Catálogos de Especialidades Farmacéuticas (Catalogues of Pharmaceutical Products) published by the Consejo General de Colegios Oficiales de Farmacéuticos (General Board of Official Associations of Pharmacists).⁵

Consumption data were obtained from the ECOM database of the Ministerio de Sanidad y Consumo (Ministry of Health and Consumer Affairs). This database contains information on the consumption and cost of the medications dispensed by pharmacies and covered by the National Health Service of Spain. It does not include in-hospital consumption, consumption paid by the patient or private insurers, or consumption of non-prescription drugs or drugs not covered by the National Health Service.⁶

The antihypertensive drug sales data for 1995-2000 provided by IMS Health Spain (International Marketing Services) were used to estimate consumption outside the National Health System. This report includes pharmacy purchases from pharmaceutical companies and distributor warehouses. All pharmacy purchases were assumed to result in sales. The difference between total consumption and drugs paid by the National Health System was considered private consumption.

The study period analyzed was 1995-2001 and all antihypertensives pertained to one of the seven major therapeutic groups, with the following subgroups:

1. Diuretics:
 - C03A and C03B. Low-ceiling diuretics, plain.
 - C03C. High-ceiling diuretics, plain.
 - C03D. Potassium-sparing agents, plain.
 - C03E. Diuretics and potassium-sparing agents in combination.
2. Beta blocking agents (BBs):
 - C07A A. Non-selective beta blocking agents, plain.
 - C07A B. Selective beta blocking agents, plain.
 - C07A G. Alpha and beta blocking agents.
 - C07B, C07C and C07D. Beta blocking agents and diuretics.
 - C07F. Beta blocking agents and other

TABLE 1. Antihypertensive Drugs Available in Spain (1995-2002)

	1995	1996	1997	1998	1999	2000	2001	2002
Active ingredients and fixed-dose combinations	91	88	87	95	97	100	98	96
Medications	203	210	214	239	254	278	304	321
Packages	409	431	434	492	538	587	649	696
Generics	—	—	—	26	40	84	143	196

antihypertensives.

3. Calcium channel blockers:

– C08: C08C and C08D. Calcium channel blockers (only those with an indication of antihypertensives).

4. ACE inhibitors:

– C09A. ACE inhibitors, plain.

– C09B A. ACE inhibitors and diuretics.

– C09B B. ACE inhibitors and calcium channel blockers.

5. Angiotensin II antagonists (ARBs):

– C09C. Angiotensin II antagonists, plain.

– C09D. Angiotensin II antagonists, combinations.

6. Alpha-adrenoreceptor antagonists:

– C02CA. Alpha-adrenoreceptor antagonists.

7. Other antihypertensives.

– C02A. Antiadrenergic agents, centrally acting.

– C02D. Arteriolar smooth muscle, agents acting on.

– C02L. Antihypertensives and diuretics in combination.

The data were expressed in defined daily doses (DDD) per 1000 inhabitants and day (DDD/1000), using the DDD values proposed by the WHO.^{7,8} For active ingredients not included in the World Health Organization's Anatomical Therapeutic Chemical (ATC) class and for fixed-dose combinations, the dose recommended by the company holding the marketing authorization was used as the DDD. Conversion was done with the following formula:

$$\text{No. DDD/1000} = \frac{\text{No. of packages dispensed} \times \text{No. of mg per dose}}{\text{doses per package} \times 1000 \text{ inhabitants/DDD in mg} \times \text{No. of inhabitants in the geographic area for the year} \times 365 \text{ days}}$$

For the calculations, the census projections and estimates for the population published by the Instituto Nacional de Estadística (National Statistics Institute) (www.ine.es) were used.⁹

Total expenditures for these medications were also

TABLE 2. DDD/1000 Consumption of 19 Subgroups of Antihypertensive Agents. ECOM Data*

	1995	1996	1997	1998	1999	2000	2001
Antiadrenergic agents, centrally acting	0.3	0.2	0.2	0.2	0.3	0.3	0.3
Alpha blocking agents	1.1	1.7	2.3	2.8	3.3	4.4	5.4
Direct vasodilators	0.0	0.0	0.0	0.1	0.1	0.1	0.1
Diuretics and antihypertensives in combination	0.9	0.7	0.6	0.5	0.4	0.3	0.3
Low-ceiling diuretics, plain	12.5	13.2	13.4	13.8	14.3	15.0	15.6
High-ceiling diuretics, plain	6.0	6.7	7.5	8.4	9.4	10.5	11.6
Potassium-sparing agents, plain	1.5	1.6	1.7	1.7	1.8	2.1	2.2
Diuretics and potassium-sparing agents in combination	10.7	10.8	10.6	10.4	10.1	9.9	9.5
Non-selective BBs, plain	0.8	0.9	0.9	0.9	0.9	1.0	0.9
Selective BBs, plain	6.0	6.6	7.2	7.8	8.5	9.6	10.6
Alpha and beta blocking agents	0.2	0.3	0.5	0.7	0.9	1.1	1.4
BBs and diuretics	1.6	1.7	1.7	1.7	1.7	1.8	1.8
BBs and other antihypertensive agents	0.2	0.2	0.3	0.6	0.6	0.6	0.6
CCBs	25.5	28.0	29.3	30.1	30.9	31.7	32.1
ACE inhibitors, plain	40.4	43.9	47.1	48.6	50.0	52.2	53.6
ACE inhibitors and diuretics	5.5	6.6	7.8	9.0	9.7	10.1	10.2
ACE inhibitors and CCBs	—	—	0.1	0.6	0.7	0.8	1.0
ARBs, plain	—	0.3	0.9	3.5	9.4	16.0	21.1
ARBs in combination	—	—	0.1	0.4	1.2	2.5	4.6
Total	113.1	123.2	132.2	141.8	154.3	169.9	182.8

*DDD/1000 indicates defined daily doses per 1000 inhabitants and day; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BBs, beta-blockers; CCBs: calcium channel blockers

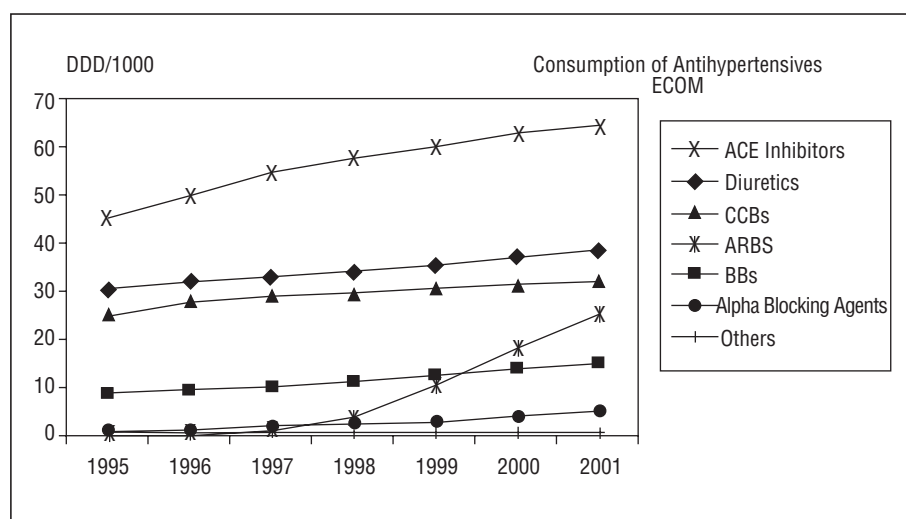


Figure 1. Antihypertensive consumption in Spain (1995-2001). ECOM database. ACE inhibitors indicates angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers; ARBs, angiotensin II receptor blockers; BBs, beta-blockers; DDD/1000, defined daily doses per 1000 inhabitants and day.

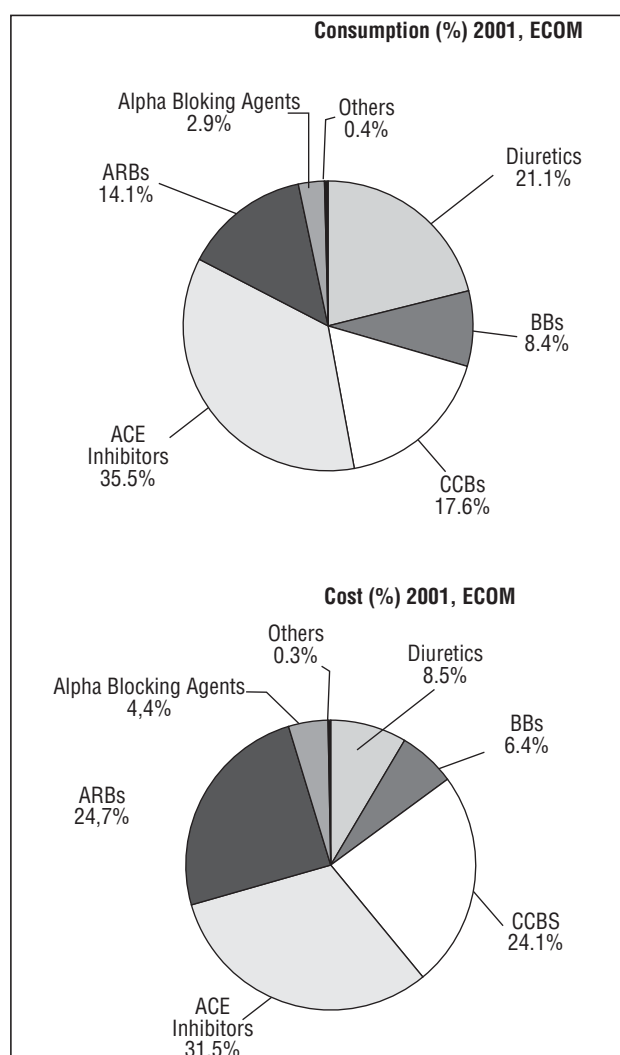


Figure 2. Consumption (%) and costs for the various antihypertensive groups in 2001 ECOM database. ARBs indicates angiotensin II receptor blockers; BBs, beta-blockers; ACE inhibitors, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

estimated for this study in both current euros for the year under consideration and in constant euros (i.e., after adjusting for inflation). This was done by using cost of living data provided by the Instituto Nacional de Estadística (www.ine.es).¹⁰ Total costs were estimated by multiplying the number of packages of each product by the price for each one. Cost per day was calculated by dividing the total cost by the total DDD consumed for the active ingredient or subgroup considered.

RESULTS

The trends for antihypertensives available during the study period (Table 1) indicate little change in the number of active ingredients and fixed-dose combinations available (91 in 1995 vs 96 in 2002, a 5.5% increase) but a sharp increase in the number of proprietary products (203 vs 321, a 58.1% increase) and in the number of different pharmaceutical presentations (409 vs 696, a 70.2% increase).

Antihypertensives covered by the National Health Service went from 113.1 DDD/1000 in 1995 to 182.8 in 2001 (61.6% increase). The use of ACE inhibitors rose steadily until 1997 and leveled out afterward, whereas the use of ARBs climbed sharply after their introduction in 1996 (Figure 1; Table 2). The pattern of use and the costs of antihypertensives in 2001 are shown in Figure 2. The most commonly used active ingredients in 2001 were enalapril (28.9 DDD/1000), amlodipine (13.3 DDD/1000), furosemide (8.3 DDD/1000), amiloride + hydrochlorothiazide combination (7.8 DDD/1000), captopril (7.8 DDD/1000), atenolol (6.8 DDD/1000), nifedipine (6.5 DDD/1000), candesartan (5.6 DDD/1000), and doxazosin (5.3 DDD/1000).

During the study period, the drugs with the largest increases in consumption were enalapril (10.1 DDD/1000), amlodipine (8.9 DDD/1000), candesartan

TABLE 3. Costs of Antihypertensive Therapy by Therapeutic Subgroup (1995-2001). ECOM Database. In Millions of Euros*

	1995	1996	1997	1998	1999	2000	2001
Antiadrenergic agents, centrally acting	1.0	0.8	0.7	1.1	1.7	2.3	2.4
Alpha blocking agents	13.0	20.6	27.2	32.8	37.7	43.8	50.4
Arteriolar smooth muscle, agents acting on	0.2	0.2	0.2	0.2	0.2	0.2	0.3
Diuretics and antihypertensives in combination	1.2	1.0	0.8	0.7	0.5	0.5	0.4
Low-ceiling diuretics, plain	12.7	13.8	14.2	16.1	19.9	22.8	26.2
High-ceiling diuretics, plain	10.9	17.6	23.0	28.7	35.7	42.3	50.9
Potassium-sparing agents, plain	5.6	5.9	6.1	6.4	6.6	7.0	7.6
Diuretics and potassium-sparing agents	15.2	15.2	14.5	14.3	13.6	13.1	12.7
Non-selective BBs, plain	3.4	3.6	3.8	4.1	4.3	4.3	4.4
Selective BBs, plain	22.4	24.8	25.7	27.6	31.1	35.1	37.1
Alpha and beta blocking agents	2.5	4.0	7.0	10.1	13.2	15.4	18.7
BBs and diuretics	7.7	8.0	7.9	8.1	8.1	8.1	8.3
BBs and other antihypertensives	0.4	0.3	1.9	4.9	5.2	5.0	5.4
CCBs	223.3	251.6	259.6	268.7	274.5	272.9	276.4
ACE inhibitors, plain	276.9	298.2	304.4	304.5	301.5	294.8	259.1
ACE inhibitors and diuretics	50.4	60.8	70.0	81.5	87.4	88.0	89.0
ACE inhibitors and CCBs	—	—	1.8	7.5	9.7	10.6	12.8
ARBs, plain	—	3.7	13.5	48.9	107.5	159.4	210.4
ARBs in combination	—	—	0.8	5.9	17.5	35.5	72.5
Total	646.4	730.1	783.1	871.9	975.6	1060.9	1144.7

*ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BBs, beta-blockers; CCBs, calcium channel blockers

(5.6 DDD/1000), valsartan (5.0 DDD/1000), and doxazosin (4.4 DDD/1000). In contrast, the active ingredients with the largest drop in consumption were nifedipine (−2.8 DDD/1000), captopril (−2.1 DDD/1000), nitrendipine (−0.9 DDD/1000), benazepril (−0.6 DDD/1000) and the amiloride + hydrochlorothiazide combination (−0.6 DDD/1000). Regarding therapeutic subgroups, this increase was largely due to plain ARBs (21.1 DDD/1000), plain ACE inhibitors (13.2 DDD/1000), and CCBs (6.6 DDD/1000).

For all antihypertensive drugs, the cost expressed in euros climbed from 646.42 million euros in 1995 to 1144.77 million in 2001, an increase of 77.1%. In constant euros, the cost increase was 50.9%. Not all groups showed the same trends; in the last two years studied, ACE inhibitor costs decreased, while CCB costs remained steady and costs for other groups, particularly ARBs, rose. The latter group accounted for 24.7% of all costs in 2001 (Figure 2 and Table 3). Figure 3 shows the cost trends for each therapeutic group.

Figure 4 indicates the trend in cost per day for the various therapeutic groups of antihypertensive agents, expressed in current euros, as taken from the ECOM data. The cost per day for all antihypertensives went from 0.40 euros in 1995 to 0.43 euros in 2001, an increase of 7.5% (Table 4). Expressed in 1995 current money, the cost per day went from 0.40 to 0.36 euros, a decrease of 9%.

The values for antihypertensive consumption using

IMS data were 127.1 DDD/1000 in 1995 and 189.9 DDD/1000 in 2000—IMS data for 2001 are not available—, with a mean difference between the two sources of information of 12.4%. The subgroups showing the largest differences were antihypertensives and diuretics in combination (39.8%) and plain non-selective BBs (25.5%). The subgroups with the smallest differences were plain ACE inhibitors (8.0%), ACE inhibitors and diuretics (10.4%), and CCBs (10.9%). Plain ARBs (16.2%), ARBs in combination (16.8%), plain low-ceiling diuretics (18.9%) and plain high-ceiling diuretics (21.1%) had intermediate consumption levels.

DISCUSSION

During the period studied in Spain, there has been a major shift in the antihypertensive drugs available and the consumption pattern for these agents resulting from the new medication groups placed on the market and from new active ingredients in existing groups. In terms of the agents available, there was a much higher increase in the number of medications and types of packages than in the number of authorized active ingredients and fixed-dose combinations involving basically three groups: ACE inhibitors, CCBs and ARBs. This is largely explained by the greater availability of generic medicines, a phenomenon accounting for two-thirds of the increase, and by new active ingredients now on the market: moxonidine, torasemide, nebivolol, lercanidipine, barnidipine,

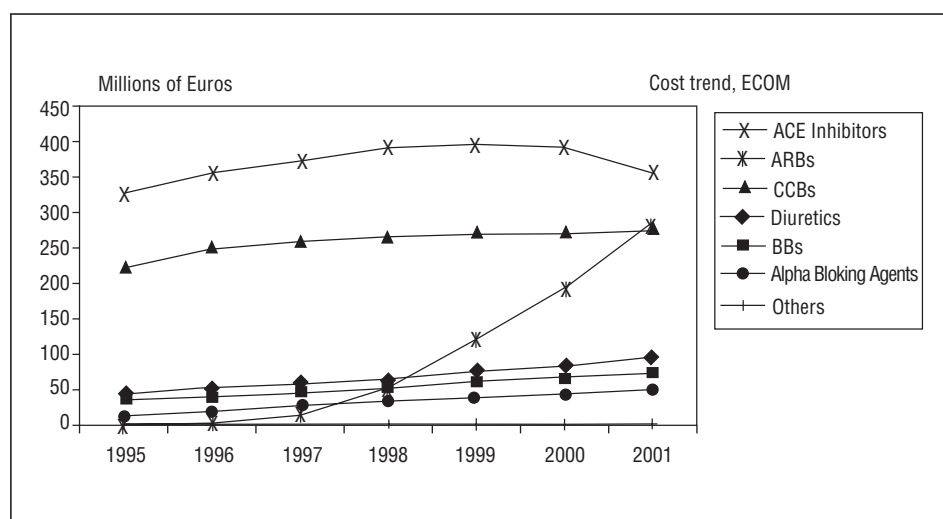


Figure 3. Cost trends for the major groups of antihypertensives (1995-2001). ECOM database. ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; BBs, beta-blockers.

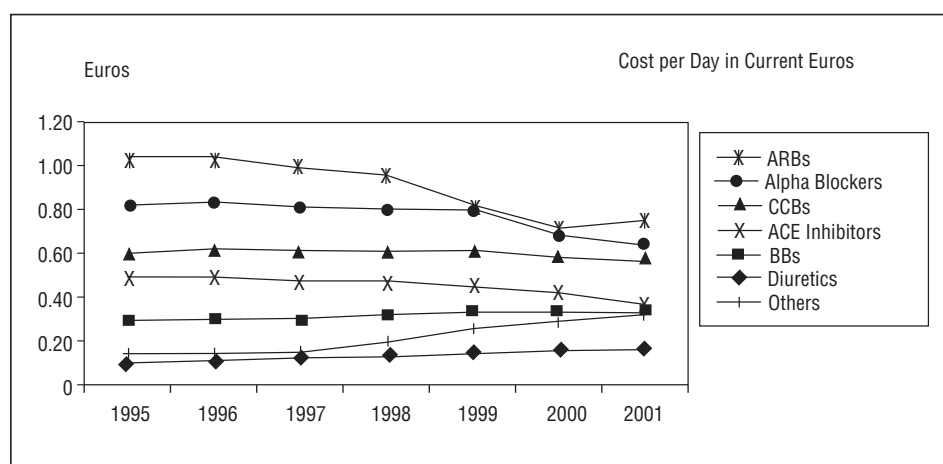


Figure 4. Cost per day of therapy in current euros for the various major antihypertensive groups. ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; BBs, beta-blockers.

spirapril, and particularly, ARBs (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, and their combinations with hydrochlorothiazide). The proliferation of “me-too” drugs also occurs in this case (e.g., 11 ACE inhibitors or 6 ARBs), although their potential to contribute to a more rational use is rather doubtful and only adds confusion in every step along the drug chain.¹¹

Based on the ECOM database, the consumption of antihypertensives in Spain for the 7 years studied increased 61.7%. These data indicate that more patients with hypertension are receiving therapy, although the increase in use does not necessarily imply better control of hypertension.¹² Two decades ago antihypertensive usage in Spain was below that of other European countries,¹³ but has now reached similar levels. In 2000, Norway used 194 DDD/1000, a level similar to the 189.9 DDD/1000 observed in Spain according to the IMS database for the same year. Although consumption is similar, the pattern of use differs: in Norway, BBs are used more frequently

and ACE inhibitors less frequently. In 2000, the proportions of antihypertensives used in Norway were the following: ACE inhibitors (24%), CCBs (21%), diuretics (21%), BBs (17%), ARBs (12%), and others (5%).¹⁴

In the National Health System, the total cost of antihypertensives has increased considerably (77%), although the increase is lower (51%) in constant currency. If these data are compared with the total costs at retail price of drugs covered by the National Health System (801 180 million pesetas in 1995 and 1 334 307 million pesetas in 2001), the cost of antihypertensive therapy has risen from 13.4% to 14.3% of all pharmaceutical expenditure by this system.

In absolute financial terms and assuming that all drugs are equally effective, diuretics have the best efficiency profile; although consumption accounts for 21.2% of the total amount, costs are only 8.5% of the total, with a mean cost per day of 17 eurocents in 2001. Unlike other countries, diuretics are still widely accepted in Spain. In fact, the use of thiazides is

TABLE 4. Weighted Mean Cost per Day for the 19 Antihypertensive Subgroups, Expressed in Current Euros

	1995	2001	Increase (%)
Antiadrenergic agents,	0.27	0.49	81.5
centrally acting			
Alpha blocking agents	0.82	0.64	-22.0
Arteriolar smooth muscle,	0.33	0.32	-3.0
agents acting on			
Diuretics and antihypertensives	0.10	0.10	0.0
in combination			
Low-ceiling diuretics, plain	0.07	0.11	57.1
High-ceiling diuretics, plain	0.13	0.30	130.8
Potassium-sparing agents, plain	0.27	0.24	-11.1
Diuretics and potassium-sparing	0.10	0.09	-10.0
agents			
Non-selective BBs	0.28	0.31	10.7
Selective BBs, plain	0.26	0.24	-7.7
Alpha and beta blocking agents	0.93	0.89	-4.3
Diuretics and alpha blocking	0.33	0.31	-6.1
agents			
BBs with other antihypertensives	0.15	0.58	286.7
CCBs	0.61	0.59	-3.3
ACE inhibitors, plain	0.48	0.33	-31.3
ACE inhibitors and diuretics	0.64	0.59	-7.8
ACE inhibitors and CCBs	0.94 [†]	0.87	-7.5
ARBs, plain	1.04 [‡]	0.68	-34.6
ARBs in combination	1.00 [†]	1.07	7.0
Weighted mean	0.40	0.43	7.5

[†]In the year the drugs were placed on the market (1997). [‡]In the year the drugs were placed on the market (1996). [†]BBs indicates beta-blockers; CCBs, calcium channel blockers; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

dropping worldwide,^{15,16} whereas overall use has been slowly but steadily increasing in Spain. Traditionally, thiazide diuretics are associated with adverse effects on glucose, lipid, uric acid, potassium, and creatinine levels. However, these adverse effects are often the result of excessively high doses,¹⁷⁻¹⁹ and are therefore avoidable. The use of diuretics in Spain can be considered favorably in light of the new JNC VII, European and Spanish clinical guidelines for hypertension, in which diuretics are recognized as first-line therapy.²⁰⁻²⁴

In 2001, BBs represented 8.4% of consumption and the respective costs accounted for 6.5% of the total (73.8 million euros), with a mean cost per day of 0.32 euros, below the mean of 0.43 euros for all antihypertensives. In comparison with other countries, BBs still have a low acceptance in Spain, possibly because of their adverse effect profile or certain contraindications because of associated disease.^{25,26}

In contrast, CCBs accounted for 17.6% of all antihypertensives in 2001, whereas costs rose to 24.1%, representing 276.47 million euros at retail price. Controversies about their safety have basically affected nifedipine.^{27,28} The trend in consumption of this drug has decreased in parallel to these

controversies (dropping from 9.28% to 6.47 DDD/1000). In contrast, amlodipine was the antihypertensive with the second greatest growth and the second most consumed in 2001. At present some authors consider them clear front-line drugs for primary prevention of cardiovascular events, with a clear advantage in stroke prevention.²⁹ However, others consider them less attractive, as they entail greater risk of acute myocardial infarction, heart failure and cardiovascular mortality than other groups, with a slight advantage in stroke prevention.³⁰ Nevertheless, the latest guidelines include them as first-line medications and highlight their efficacy in elderly patients who have high systolic blood pressure, either alone or associated with diabetes.²⁰

The contribution of ACE inhibitors to use (35.5%) is similar to cost (31.5%), with a weighted average for cost per day of 0.38 euros. These antihypertensives showed higher consumption, but were also the most affected by the introduction of ARBs. Their total costs in current money and in the 7 years studied grew only 10%, and they presently show a downward trend. Along with diuretics and beta-blockers, they are a good example of efficiency in the clinical use of antihypertensives.

The introduction of ARBs has had a considerable impact, in terms of both consumption and cost. In 2001 they accounted for 14% of consumption (25.7 DDD/1000 in 2001) and almost 25% of total costs (282.48 million euros). They have many characteristics in common with ACE inhibitors, with the main difference being the absence of cough as a side effect and a probable lower incidence of angioneurotic edema. All other adverse effects of ACE inhibitors can also be observed with ARBs.³¹ Because of their higher cost (cost per day was 75 eurocents for 2001), the guidelines³¹⁻³³ tend to recommend them when replacing ACE inhibitors that are not tolerated because of cough, although the high increase in consumption may indicate that in actual clinical practice, ARBs are not reserved for these situations. The decrease in cost per day during the study period results from the introduction of less expensive drugs and the decrease in price for existing drugs.

The consumption of alpha blockers, particularly doxazocin, was 5.3 DDD/1000 in 2001, with costs of 50.15 million euros and a cost per day of 0.65 euros. The WHO-ISH (1999)³² or MSyC guidelines (1996)³⁴ classify it as a front-line therapy for hypertension, particularly when the patient has benign prostatic hypertrophy or dyslipidemia. In recent years, emerging evidence has questioned the use of these drugs as front-line therapy, however.³⁵ In any case, the accumulating scientific evidence seems to be inconsistent with the increase in consumption, which is 450% for the period studied. These drugs are not mentioned in the recent JNC VII,²³ and the Sociedad

Española de Cardiología guidelines on hypertension refers to them as controversial.²⁰

Another aspect of interest is the increased consumption of fixed-dose combinations (18.9 DDD/1000 in 1995 vs 28.1 DDD/1000 in 2001), primarily as the result of medications in which ACE inhibitors or ARBs are combined with hydrochlorothiazide. The additional advantages of fixed-dose formulations were recognized by the JNC VI in 1997³³ and the WHO-ISH in 1999,³² as well as the SEH-LELHA 2002³¹ in Spain. These guidelines acknowledge that apart from the add-on hypotensive effect, the combinations also have reduced adverse effects, prolonged antihypertensive effects, improved patient compliance and the possibility to use lower doses. Because of the high percentage of patients who require combined therapy, and the advantages of these drugs,³⁶ the upward trend can be considered a positive change. The advantages of these combinations have been recently recognized in the Sociedad Española de Cardiología guidelines,²⁰ the JNC VII²³, and the European Society of Cardiology guidelines.²⁴

The data obtained from the ECOM database are somewhat limited, as they do not include prescriptions for health maintenance organization members or direct sale. Furthermore, they do not consider in-hospital consumption or medications not paid for by the National Health System. If we assume that the IMS data indicate actual consumption, then 12.4% of total consumption of antihypertensives took place outside the National Health System. Moreover, when a medication is introduced to the market, pharmacies must purchase an initial supply, a factor which must be taken into account when analyzing larger differences for recently available drugs. The differences are even larger for the less expensive subgroups. Private consumption or illegal over-the-counter delivery at pharmacies is less estrained with these medications, although there would be some limits when using more expensive drugs.

Limitations of the Study

The limitations of this study mainly concern the method used to calculate consumption. The DDD is an approximate unit of measurement and does not necessarily reflect the daily dose consumed. For instance, the DDD for enalapril is 10 mg, whereas the medications most commonly used in Spain contain 20 mg per dose. In these cases, the use of DDD leads to an overestimation of the active ingredients.³⁷ There are also cases (e.g., indapamide) in which consumption is underestimated: the "delayed-release" forms are among those most commonly used, with a recommended dose of 1.5 mg a day, whereas the DDD of the ATC is established as 2.5 mg a day.

Some of the medications considered in this study are also used for other common indications, such as

heart failure, angina pectoris, etc. Thus, we cannot assume from the study data that all the drugs were used exclusively for hypertension. However a, previous study estimated that, except for loop diuretics (not included in this study), propranolol and diltiazem, all other medications were used primarily for hypertension.³

Thirdly, the data contains no information on compliance with therapy; and therefore the term "consumption" is used figuratively, and at no time can we assume that the medication dispensed was actually consumed.

Lastly, changes in the therapeutic approach used with hypertension in recent years should be taken into consideration. The new objectives to decrease blood pressure in growing populations, such as diabetes patients, the need to use drug combinations in many of these patients, as well as new evidence and recommendations that support the use of some of the new antihypertensive agents (e.g., ARBs in patients with type 2 diabetes and kidney disease),²⁰ have contributed to the increase in consumption.

CONCLUSIONS

The use of antihypertensive agents has increased considerably in Spain during the period studied, a favorable situation, given the inadequate treatment of high blood pressure in Spain. Some of the aspects studied indicate that the use of these drugs is more rational than in previous years, although there continue to be differences between the use of the various classes of antihypertensive agents and the scientific evidence that back their use. In terms of economics, the differences between usage and costs reveal critical issues for intervention aimed at improving efficiency in the therapies.

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