Use of Antihypertensive Drugs in Spain (1995-2001)
Javier García del Pozo, Eduardo Ramos Sevillano, Francisco J. de Abajo, Ramona Mateos Campos

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.

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
secondary cause of 50% of all cardiovascular diseases worldwide. 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.

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%.

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.

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). 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.

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...

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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-adrenergic antagonists:
   – C02CA. Alpha-adrenergic agents.

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. 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:

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

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. Total expenditures for these medications were also

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

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<td>132.2</td>
<td>141.8</td>
<td>154.3</td>
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*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
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). 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 doxazocin (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

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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.
(5.6 DDD/1000), valsartan (5.0 DDD/1000), and
doxazocin (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 cons-
tant 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 diure-
tics (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,

of Euros**

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

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

1In the year the drugs were placed on the market (1997). 2In 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, 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 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.

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.

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. 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, amldipine 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. 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. 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.

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. Because of their higher cost (cost per day was 75 eurocents for 2001), the guidelines 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) or MSyC guidelines (1996) 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. 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 and the Sociedad...
限制作为空

限制性的研究

研究所涉及的限制主要涉及使用药物的计算方法。DDD（日剂量单位）是药物单位量的近似值，但是这并不完全反映实际的使用量。例如，对于阿替洛尔的DDD是10 mg，但是实际上每天使用的药量可能是20 mg。在这种情况下，DDD的使用会导致对活性成分的过度估计。37 还有其他情况下（如，吲达帕胺）在消费中的估计被低估了：延迟释放形式是被高估的。38

一些药物在本研究中被用于其他常见的适应症，例如，ACE抑制剂或ARBs是与心力衰竭，冠心病，等。因此，我们不能假设从研究数据中所有药物均被用于唯一的一个适应症。然而，先前的研究估计，除了利尿剂（不包括在本研究中），普普洛尔和地尔硫卓，所有其他药物均用于主要的高血压。3 第三，数据包含没有足够的信息，需要在治疗中使用药物；而且，术语“使用”是被引申的，没有时间可以假定所使用的药物实际被使用。

最后，对于抗高血压药物在近期内的使用应该是被考虑的。新的目标是减少在快速增长的人口中的高血压，如糖尿病患者，需要使用药物的组合，以满足这些患者，以及新证据和推荐的使用其中一部分的新的抗高血压药物（例如，ARBs在患者中型2糖尿病和肾病），20 有助于增加了消耗。

结论

抗高血压药物的使用在西班牙在研究期间增加，这表明了一个有利的情况，给与了这些药物的不适当的治疗的高血压。然而，继续存在使用药物的差距，这在一些使用药物的组合中可以被看到，以及科学证据表明它们的使用。

参考文献

including Defined Daily Doses (DDDs) for plain substances. Oslo: WHO CCDSM, 2001; p. 48-62.