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# *COST OF POOR ADHERENCE TO ANTI-HYPERTENSIVE THERAPY IN 5 EUROPEAN COUNTRIES*

## ABSTRACT

**Background:** The financial burden for EU health systems associated with cardiovascular disease has been estimated to be nearly € 110 billion in 2006, corresponding to 10% of total healthcare expenditure across EU or a mean € 223 annual cost per capita. The main purpose of this study is to estimate the costs related to hypertension and the economic impact of increasing adherence to anti-hypertensive therapy in 5 European countries (Italy, Germany, France, Spain and England).

**Methods:** A probabilistic prevalence-based decision tree model was developed to estimate the direct costs of cardiovascular disease related to hypertension (CV defined as: stroke, heart attack, kidney disease, heart failure) in 5 European countries. Our model considered adherence to hypertension treatment as a main driver of blood pressure control (BP < 140/90 mmHg). Relative risk of CV, based on controlled or uncontrolled BP group, was estimated from the Framingham Heart Study and national review data. Prevalence and cost data were estimated from national literature reviews. A National Health System (NHS) perspective for 10 years was considered. Probabilistic Sensitivity Analysis (PSA) was performed in order to evaluate uncertainty around the results (given as 95% confidence intervals).

**Results:** The model estimated a total of 8.6 million (1.4 in Italy, 3.3 in Germany, 1.2 in Spain, 1.8 in France and 0.9 in England) CV events related to hypertension over the 10 year time horizon. Increasing the adherence rate to anti-hypertensive therapy to 70% (baseline value is different for each country) would lead to 82,235 fewer CV events (24,058 in Italy, 7,870 in Germany, 18,870 in Spain, 24,855 in France and 6,553 in England). From the NHS perspective, the direct cost associated with hypertension was estimated to be € 51.1 billion (8.1 in Italy, 17.8 in Germany, 12.2 in Spain, 8.8 in France and 4.1 in England). Increasing adherence to anti-hypertensive therapy to 70% would save a total of € 323.7 million (CI 95%: € 304.2 - € 342.2 million) from the NHSs perspective.

**Conclusion:** This study is the first attempt to estimate the economic impact of non-adherence amongst patients with diagnosed hypertension in Europe, using data from five European countries (Italy, France, Germany, Spain and England).

## Introduction

Safe and effective treatments for a range of health issues are widely available in Europe. These treatments, however, are not always used to their full potential. They can be limited by many factors, including a lack of adherence to treatment. The reasons behind low adherence are complex, and can include a variety of factors (such as socio-economic status, patient beliefs and lifestyle, health-literacy) and their interaction with the health care system.

Better adherence to medical treatment, as well as medical and prevention plans, will improve the quality of life of patients and help support the long term sustainability of health care systems.<sup>1</sup>

In Europe, about 4.58 million people die every year due to cardiovascular diseases (CV)<sup>2</sup>. In the 25 European countries, the annual expenditure for the treatment of CVs is estimated to be about € 169 billion<sup>3</sup>. Of this, about 61% is attributable to direct healthcare costs.

The treatment of hypertension, one of the main risk factors, reduces the number of adverse cardiovascular events and thus decreases the economic and health impact of hypertension related CV<sup>4, 5, 6</sup>. The effectiveness of therapies used to treat hypertension has been shown to be closely related to the patients' medical adherence to treatment<sup>7, 8</sup>. A level of good adherence needed for a pharmacological treatment to be effective, is widely recognized to be around 80% of the prescribed therapy<sup>9</sup>. Existing research shows that in several European countries less than 60% of treated hypertensive subjects have an adherence to their treatment over 80%<sup>10,11,12,13,14</sup>. Poor adherence results in severe losses in terms of clinical efficacy and economic efficiency, especially as the cardiovascular events that full adherence could avoid translate into greater hospitalization costs.

Non-adherence to anti-hypertensive drugs remains a global issue and one of the main clinical obstacles to the reduction of cardiovascular morbidity and mortality. One study<sup>15</sup> has estimated that in the United States 100% adherence to treatment could reduce the risk of CV by 32%, with 8.5 million fewer events over 10 years follow-up and cumulative savings to the health care system of \$ 72 billion<sup>15</sup>. To date this is the only systematic analysis published, but its results cannot be transferred directly to Europe, since there exist considerable variations in healthcare systems both between the United States and Europe, and between different European countries. The main purpose of this study is therefore to estimate the total cost of CV related to hypertension and the economic impact

of non-adherence to medical anti-hypertensive therapy in five European countries (England, France, Germany, Italy and Spain).

## Methods

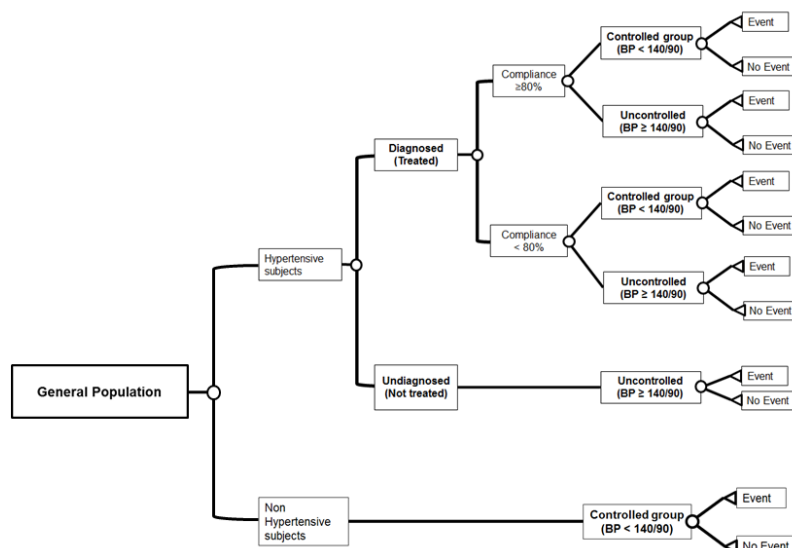
### Model

A prevalence based probabilistic model was developed to estimate the costs and consequences of CV, using risk equations to estimate the risk of cardiovascular events based on the Framingham Heart Study. The model simulates the natural history of the disease, where patients residing in each of the countries included in the analysis may or may not be hypertensive (Figure 1). Hypertensive patients (BP  $\geq 140/90$ ) may or may not be diagnosed with hypertension. The model assumes that all diagnosed patients are treated and that adherence to treatment (defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen<sup>16</sup>) is the main driver for the patient to achieve a controlled blood pressure (BP  $< 140/90$ ) and consequently a lower probability of experiencing a cardiovascular event.

The model assumes that all undiagnosed hypertensive patients have an uncontrolled BP while the non-hypertensive subjects maintain a BP  $< 140/90$ . On the basis of the Framingham<sup>17</sup> risk equations, all subjects, including those who are not hypertensive, have a defined probability of experiencing a CV event.

The model is used to produce a risk estimate over a 10 year period. Costs are estimated from a health system perspective using demographic, epidemiological and economic data obtained from national and international literature for each country included in the analysis.

Figure 1 - Decision Tree Model



## Cardiovascular Disease (CV) event

The cardiovascular risk equation reported by D'Agostino et al. (2008)<sup>17</sup> produces estimates of the risk of CV which varies depending on the patient's age and other demographic characteristics, on clinical parameters including BP and on other risk factors. In our model the population has been divided into 4 risk groups: diagnosed subjects with controlled BP (BP < 140/90) after treatment, diagnosed subjects with uncontrolled BP (BP ≥ 140/90) after treatment, hypertensive but undiagnosed subjects (BP ≥ 140/90) and healthy subjects (BP < 140/90). Within each risk group, the composition by age of the population of each country included in the analysis (Appendix A) was considered.

The sum of cardiovascular risk scores, by BP risk group and age-weighted, produced the 10-year CV event probabilities shown in Table 1.

In order to estimate the costs of CV events attributable to hypertension, we considered a percentage of CV events that was assumed (by literature review) related to hypertension (Appendix B table B-1)<sup>15</sup>. As the focus of this study relates to costs of hypertension and non-adherence to therapy, healthy subjects were not considered in our cost analysis.

*Table 1 –10 year CV event probability by risk group and country of residence (age-weighted)*

Risk group	ITALY	GERMANY	SPAIN	FRANCE	ENGLAND
Diagnosed Controlled → Hypertension Event (FEMALE)	4.50%	4.50%	4.50%	4.50%	4.50%
Diagnosed Uncontrolled → Hypertension Event (FEMALE)	10.00%	10.00%	8.60%	10.00%	10.00%
Diagnosed Controlled → Hypertension Event (MALE)	9.40%	9.40%	7.90%	9.40%	7.90%
Diagnosed Uncontrolled → Hypertension Event (MALE)	13.20%	15.60%	13.20%	13.20%	13.20%
Undiagnosed Uncontrolled → Hypertension Event (FEMALE)	10.00%	10.00%	8.60%	10.00%	10.00%
Undiagnosed Uncontrolled → Hypertension Event (MALE)	13.20%	15.60%	13.20%	13.20%	13.20%
Untreated Controlled → Hypertension Event (FEMALE)	3.30%	3.30%	3.30%	3.30%	3.30%
Untreated Controlled → Hypertension Event (MALE)	6.70%	6.70%	5.60%	6.70%	5.60%

Processing of the Framingham Heart Study by the authors<sup>17</sup>.

## Demographic and epidemiological data

Demographic and epidemiological parameter values for each country are included in the analysis, and information about the prevalence of diagnosed and undiagnosed to

hypertension and treatment adherence were obtained from national and international literature: values and sources are reported in Table 2.

*Table 2 – Demographic and epidemiological parameters*

Demographic data	ITALY	GERMANY	SPAIN	FRANCE	ENGLAND
General Population	60,626,442 <sup>[18]</sup>	81,843,743 <sup>[19]</sup>	46,815,916 <sup>[20]</sup>	65,281,000 <sup>[21]</sup>	52,642,500 <sup>[22]</sup>
Percentage of Female	51.48% <sup>[18]</sup>	50.87% <sup>[19]</sup>	50.65% <sup>[20]</sup>	51.57% <sup>[21]</sup>	50.84% <sup>[22]</sup>
Percentage of Female - Age ≥ 30 years	71.76% <sup>[18]</sup>	70.86% <sup>[19]</sup>	69.37% <sup>[20]</sup>	64.76% <sup>[21]</sup>	63.54% <sup>[22]</sup>
Percentage of Male - Age ≥ 30 years	68.59% <sup>[18]</sup>	68.33% <sup>[19]</sup>	67.05% <sup>[20]</sup>	61.39% <sup>[21]</sup>	61.17% <sup>[22]</sup>
Percentage of FEMALE with hypertension - Age ≥ 30 years	31.00% <sup>[23]</sup>	50.30% <sup>[24]</sup>	31.70% <sup>[25, 26]</sup>	36.42% <sup>[27]</sup>	32.10% <sup>[28]</sup>
Percentage of MALE with hypertension - Age ≥ 30 years	33.00% <sup>[23]</sup>	60.20% <sup>[24]</sup>	44.60% <sup>[25, 26]</sup>	47.62% <sup>[29]</sup>	35.12% <sup>[28]</sup>
Percentage of diagnosed and treated hypertensive subjects	73.00% <sup>[30]</sup>	77.00% <sup>[31]</sup>	59.40% <sup>[26]</sup>	56.92% <sup>[27, 29]</sup>	58.38% <sup>[32]</sup>
Percentage of diagnosed patients with adherence ≥ 80%	41.50% <sup>[9]</sup>	66.90% <sup>[13]</sup>	39.40% <sup>[14]</sup>	39.00% <sup>[12]</sup>	56.85% <sup>[11]</sup>

### Estimate of direct healthcare costs

In accordance with the perspective of the analysis, only direct healthcare costs associated with the treatment and control of hypertension and all related CV events were considered. Regarding drug costs, two different approaches were used depending on available data for each country. The annual average cost for prescribed drugs was estimated in Italy and France from a top-down perspective as follows: annual pharmaceutical expenditure per ATC groups C02, C03, C07, C08 (antihypertensives, diuretics, beta blocking agents, calcium channel blockers), C09 (agents acting on the renin-angiotensin system), C09C, C09D (angiotensin II antagonists, plain, angiotensin II antagonists, combinations) divided by the number of treated patients as estimated by the model. For Germany, England and Spain, costs were derived from a bottom-up perspective according to estimates available in the published literature. The resulting parameter values and their sources for each country are summarised in Table 3.

Medical costs of cardiovascular events were assessed as a weighted average depending on country-specific number of events attributable to hypertension and associated hospitalization rates (Appendix B).



Table 3 - Cost parameters (mean per subjects)

	ITALY	ENGLAND	FRANCE	GERMANY	SPAIN
Drug cost	€ 280 <sup>[33]</sup>	€ 37 <sup>[34]</sup>	€ 244 <sup>[35]</sup>	€ 213 <sup>[36]</sup>	€ 974 <sup>[37]</sup>
Hospitalization cost	€ 3,939 <sup>[38]</sup>	€ 3,511 <sup>[39]</sup>	€ 3,543 <sup>[40, 41]</sup>	€ 3,786 <sup>[42, 43]</sup>	€ 4,350 <sup>[44]</sup>

### Scenarios and sensitivity analyses

The impact of improving adherence was compared against the current values for each country as reported in Table 2. In the main scenario it was assumed that the number of subjects treated and having an adherence rate to antihypertensive treatment equal or above 80%, would increased to 70% in all Countries. The model was run at current adherence levels and at 70% of treated subjects, in order to estimate the difference in CV events and related costs under the two scenarios.

Probabilistic sensitivity analysis was also carried out through Monte Carlo simulations based on a range of probabilities for each parameter considered in the model (Appendix C). Sensitivity analysis enabled the estimation of 95% confidence intervals (CI 95%) around the mean value, using the percentile method to identify the upper and lower 95% bounds over 5,000 simulations. The model and the sensitivity analysis were developed in Microsoft Excel® (Microsoft Corp., Redmond, WA).

## Results

Table 4 reports the predicted number and cost of all CV events related to hypertension for each country and aggregated across all 5 countries. Over the 10-year time horizon, a total of almost 8.6 million CV events are predicted based on current demographic, epidemiological and adherence data (32% were estimated to occur in Germany, 20% in France and Italy, and 15% and 12% in Spain and England respectively). The total cost of CV events attributable to hypertension was estimated to exceed € 51.1 billion over a time span of 10 years (range: € 4.1 in England and € 17.8 in Germany).

*Table 4 - Base case results: number and cost of CV events attributable to hypertension*

BASE-CASE	ITALY	GERMANY	SPAIN	FRANCE	ENGLAND	TOTAL
<b>Mean number of CV events</b>						
Diagnosed Subjects	934,558	2,409,410	650,129	940,998	461,025	5,396,120
Undiagnosed Subjects	424,749	934,768	552,331	867,587	425,886	3,205,321
<b>Total CV Events</b>	<b>1,359,307</b>	<b>3,344,178</b>	<b>1,202,460</b>	<b>1,808,585</b>	<b>886,911</b>	<b>8,601,441</b>
<b>Mean cost per subjects</b>						
Diagnosed Subjects	€ 1,305	€ 1,170	€ 2,709	€ 1,158	€ 704	€ 7,046
Undiagnosed Subjects	€ 914	€ 969	€ 948	€ 822	€ 815	€ 4,468
<b>Mean total cost per subject</b>	<b>€ 2,219</b>	<b>€ 2,139</b>	<b>€ 3,657</b>	<b>€ 1,980</b>	<b>€ 1,518</b>	<b>€ 11,513</b>
<b>Total Cost</b>						
Diagnosed Subjects (€ Billion)	€ 6.46	€ 14.26	€ 9.84	€ 5.72	€ 2.27	€ 38.55
Undiagnosed Subjects (€ Billion)	€ 1.67	€ 3.54	€ 2.40	€ 3.07	€ 1.87	€ 12.56
<b>Total Hypertension Cost (€ Billion)</b>	<b>€ 8.14</b>	<b>€ 17.80</b>	<b>€ 12.25</b>	<b>€ 8.79</b>	<b>€ 4.14</b>	<b>€ 51.11</b>

Considering only the costs associated with diagnosed and treated patients, drug cost is estimated, on average, to represent 37% (range: 10% in England and 71% in Spain) of the total cost of the disease and the remaining part being attributed to hospitalisations (Table 5). In Italy, a total cost related to diagnosed and treated hypertensive patients of € 6.5 billion (CI 95%: € 5.9 – 7.1 billion) was estimated over a 10 years horizon. Similarly, in France, the cost associated with hospitalization was estimated at € 3.3 billion (CI 95%: € 2.9 – 3.7 billion) and the total expenditure for diagnosed subjects amounted to € 5.7 billion (CI 95%: € 5.1 – 6.3 billion).

Total costs related to diagnosed patients were much higher in Germany and Spain than in other countries. In Germany, where the prevalence of hypertension (Table 2) and of diagnosed subjects (Table 4) were both high, total expenditure was estimated to be € 14.3 billion (CI 95%: € 12.9 – 15.5 billion). In Spain, the high cost associated with hypertensive patients was attributable to a total drug cost of € 7.0 billion (CI 95%: € 6.3 – 7.8 billion), higher than any other country and approximately three times the cost of hospitalizations (€ 2.8 billion CI 95%: € 2.5 – 3.2 billion).

In England, drug costs of just € 0.2 billion (CI 95%: € 0.2 – 0.3 billion) were particularly low, corresponding to 10.6% of the total expenditure related to hypertensive treatment and hospitalization cost. These lower drug costs reflect a high proportion of generic drugs in the total drugs used, and low generic prices in the UK.

*Table 5 – Cost of drugs and hospitalisations of patients diagnosed with hypertension*

Country	Diagnosed patient cost	Hypertension Cost		
		Mean cost	IC 95%	
ITALY	Drug Cost	€ 2,798,271,582	€ 2,513,578,090	€ 3,082,965,074
	Hospitalization cost	€ 3,698,571,798	€ 3,299,348,488	€ 4,097,795,108
	<b>Total cost</b>	<b>€ 6,496,843,380</b>	<b>€ 5,877,989,680</b>	<b>€ 7,115,697,080</b>
GERMANY	Drug Cost	€ 5,176,750,430	€ 4,652,232,211	€ 5,701,268,650
	Hospitalization cost	€ 9,176,695,193	€ 8,155,337,277	€ 10,198,053,110
	<b>Total cost</b>	<b>€ 14,353,445,624</b>	<b>€ 12,948,004,902</b>	<b>€ 15,758,886,346</b>
SPAIN	Drug Cost	€ 7,049,193,249	€ 6,328,671,948	€ 7,769,714,551
	Hospitalization cost	€ 2,843,658,554	€ 2,525,597,354	€ 3,161,719,755
	<b>Total cost</b>	<b>€ 9,892,851,804</b>	<b>€ 8,941,379,172</b>	<b>€ 10,844,324,435</b>
FRANCE	Drug Cost	€ 2,391,414,106	€ 2,145,779,748	€ 2,637,048,465
	Hospitalization cost	€ 3,341,557,203	€ 2,970,025,694	€ 3,713,088,712
	<b>Total cost</b>	<b>€ 5,732,971,309</b>	<b>€ 5,173,532,146</b>	<b>€ 6,292,410,473</b>
ENGLAND	Drug Cost	€ 241,130,763	€ 216,762,528	€ 265,498,998
	Hospitalization cost	€ 2,032,541,232	€ 1,811,853,114	€ 2,253,229,349
	<b>Total cost</b>	<b>€ 2,273,671,995</b>	<b>€ 1,945,276,478</b>	<b>€ 2,602,067,511</b>
TOTAL	Drug Cost	€ 10,607,566,882	€ 9,528,352,576	€ 11,686,781,187
	Hospitalization cost	€ 18,249,365,426	€ 16,236,564,573	€ 20,262,166,278
	<b>Total cost</b>	<b>€ 28,856,932,308</b>	<b>€ 25,944,803,205</b>	<b>€ 31,769,061,410</b>

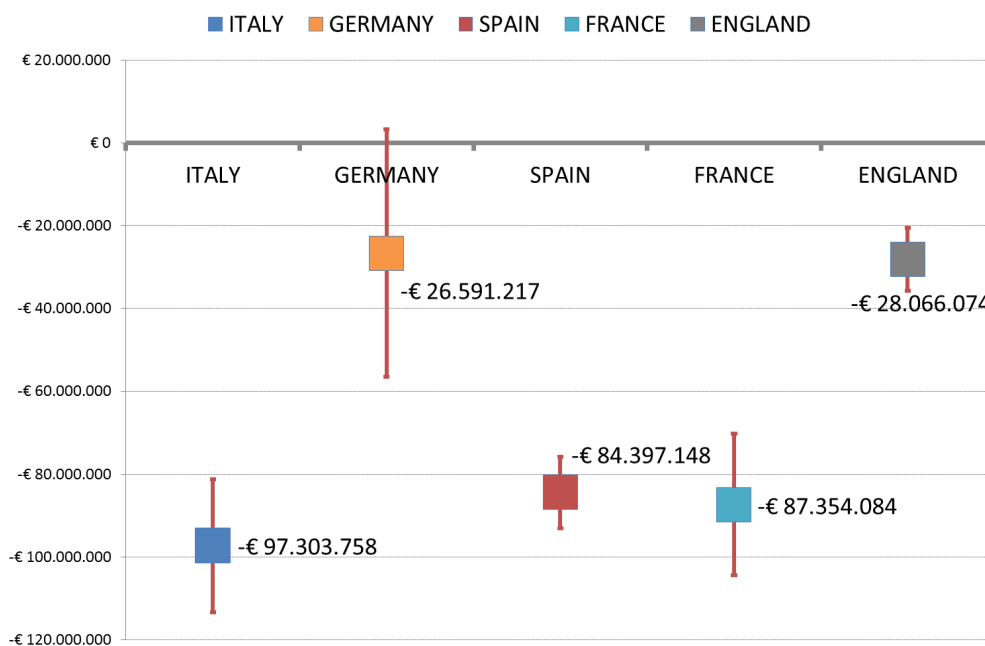
Finally, the study estimated that, by increasing to 70% the adherence to treatment in all countries, it would be possible to reduce direct healthcare costs for hypertension by about

€ 323 million (CI 95%:-€ 304, -€ 342) (Figure 2) equal to to 82,235 fewer CV events (24,058 in Italy, 7,870 in Germany, 18,870 in Spain, 24,855 in France and 6,553 in England).

By looking at savings at national level, it can be seen that countries are clustered into two groups. In the first, cost reductions due to increased adherence are in the order of € 20/30 million (Germany and England); in the second group there is a substantially higher impact of increased adherence, with cost reductions exceeding € 80 million (Italy, Spain and France). The reasons for the lower level of cost reduction in the first group differ between the two countries: Germany (average savings € 26.6 million CI 95%: -€ 56.5 - € 3.3) is characterized by adherence to treatment at the baseline (66.9%) which is already very close to the target value of 70%, whereas in England (average savings € 28.1 million CI 95%: -€ 20.4 - € 35.7) the cost of drugs is significantly lower than the European average, and therefore savings are mainly attributable to hospitalization cost.

In the second group, the quite low adherence (range: 39.0% - 41.5%) and the non-negligible costs of drugs and hospitalization determine level of savings higher than € 80 million for each of the three counties: Italy (€ 97.3 million CI 95%: -€ 81.3 - -€ 113.3), Spain (€ 84.4 million CI 95%: -€ 75.8 - -€ 92.0) and France (€ 87.4 million CI 95%: -€ 70.2 - -€ 104.5).

Figure 3 – Estimation of costs avoided due to an increase in adherence (Scenario 1 – Scenario 2) – Average and CI 95%



## Discussion and conclusion

This is the first study which aims to estimate costs associated with non-adherence to anti-hypertensive treatment in five European countries. A recent study reported that, comparing current adherence rates of approximately 40% with hypothetical full adherence of 100%, non-adherence can be estimated to entail a clinical and financial burden of over 8.5 million CV events and about \$ 72 billion in the USA<sup>15</sup> over 10 years. Our analysis assumed a more realistic scenario, in which adherence levels in the five European Countries could be increased from current levels to 70% of treated patients: in other words, a scenario where 70% of patients prescribed for an antihypertensive treatment, take at least 80% of their given regimen. Our analysis indicates that this would reduce CV-related health care costs by € 323 million (CI 95%: -€ 304 - -€ 342) over a 10 years period.

A study by Leal et al. (2006)<sup>3</sup> estimated the annual economic impact of CV through the main national sources of epidemiological and financial data. In line with our results over the course of 10 years, Leal et al. estimated an annual average expenditure of € 16.1 billion (2003) for the 5 Countries included in our analysis (drug, primary, outpatient, emergency, and inpatient care) or € 14.7 billion (2003) for outpatient and hospitalisation costs only. If one third of the total events estimated by Leal et al. are assumed to be associated with hypertension,<sup>17</sup> the total cost per year would be €4.8 billion per year, close to the € 5.1 billion (CI 95% € 4.7 - 5.5 billion) per year estimated in our study.

The present study has some limitations, mostly attributable to assumptions and estimates which were necessary to overcome the lack of standardized data for the five countries of interest. Our epidemiological data were either obtained from statistics provided by national institutions or extrapolated estimates from scientific literature. Our estimates for adherence rates were taken from a number of different studies which could have used definitions different to that given in our study<sup>16</sup>.

Likewise, costs were obtained from a number of data sources using methods and definitions which may have varied from one country to the other. This applies to both drug costs and hospital costs, which were not completely consistently derived across countries. However, use of probabilistic sensitivity analysis has allowed us to capture and explore the variability in the main parameters of the model.

The estimation of risk and of the number of CV events related to hypertension was based on a well-known cohort study - the Framingham Heart Study - that consists of a non-European population,<sup>15,17</sup> and no adjustments were made for ethnic composition in each country. However, calculations were adjusted for the age and sex structure of each population, and a 2008 study<sup>45</sup> reported a high correlation between the cardiovascular risks estimated in the Framingham study and those observed in a population of European subjects (SCORE<sup>46, 47</sup>). Indeed, the Framingham risk equations predict the risk of developing a first CV event and no assumption were considered in our analysis because of no data available.

In conclusion, our study represents the first attempt in Europe to estimate the costs associated with non-adherence to anti-hypertensive treatment, using a probabilistic prevalence based model in 5 European countries. Despite its limitations, this analysis should help decision makers to better understand the clinical and economic importance of improving adherence at national level, and will help inform strategies to improve adherence to therapy as one key issue of antihypertensive medical therapy. All actions taken to increase patient compliance to anti-hypertensive therapies, such as psychological support to enhance patient's motivation, patient's reminders, and use of fixed dose combination therapies to decrease pill burden, should be assessed by policy makers and healthcare budget holders within a framework that considers not only the short term costs of these interventions, but also possible offsetting costs due to fewer hospitalizations, and improvements in healthcare status.

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