Volume 12 • Number 6 • 2009
VALUE IN HEALTH

Cost-Utility Analysis of Eprosartan Compared to Enalapril in Primary Prevention and Nitrendipine in Secondary Prevention in Europe—The HEALTH Model

Björn Schwander, BSc,[1] Birgit Gradl, MSc,[2] York Zöllner, PhD,[2] Peter Lindgren, PhD,[3] Hans-Christoph Diener, MD,[4] Stephan Lüders, MD,[5] Joachim Schrader, MD,[5] Fernando Antoñanzas Villar, PhD,[6] Wolfgang Greiner, PhD,[7] Bengt Jönsson, PhD[8]

[1]Analytica International, Lörrach, Germany; [2]Solvay Pharmaceuticals, Hannover, Germany; [3]I3innovus, Stockholm, Sweden; [4]Department of Neurology, University Duisburg-Essen, Germany; [5]St.-Josefs-Hospital, Cloppenburg, Germany; [6]University of de la Rioja, Spain; [7]University of Bielefeld, Bielefeld, Germany; [8]Stockholm School of Economics, Stockholm, Sweden

ABSTRACT

Objective: To investigate the cost-utility of eprosartan versus enalapril (primary prevention) and versus nitrendipine (secondary prevention) on the basis of head-to-head evidence from randomized controlled trials.

Methods: The HEALTH model (Health Economic Assessment of Life with Teveten® for Hypertension) is an object-oriented probabilistic Monte Carlo simulation model. It combines a Framingham-based risk calculation with a systolic blood pressure approach to estimate the relative risk reduction of cardiovascular and cerebrovascular events based on recent meta-analyses. In secondary prevention, an additional risk reduction is modeled for eprosartan according to the results of the MOSES study ("Morbidity and Mortality after Stroke—Eprosartan Compared to Nitrendipine for Secondary Prevention"). Costs and utilities were derived from published estimates considering European country-specific health-care payer perspectives.

Results: Comparing eprosartan to enalapril in a primary prevention setting the mean costs per quality adjusted life year (QALY) gained were highest in Germany (€24,036) followed by Belgium (€17,863), the UK (€16,364), Norway (€ 13,834), Sweden (€ 11,691) and Spain (€ 7918). In a secondary prevention setting (eprosartan vs. nitrendipine) the highest costs per QALY gained have been observed in Germany (€9136) followed by the UK (€6008), Norway (€1695), Sweden (€907), Spain (€–2054) and Belgium (€–5767).

Conclusions: Considering a €30,000 willingness-to-pay threshold per QALY gained, eprosartan is cost-effective as compared to enalapril in primary prevention (patients ≥50 years old and a systolic blood pressure ≥160 mm Hg) and cost-effective as compared to nitrendipine in secondary prevention (all investigated patients).

Key words: cost-utility, eprosartan, enalapril, nitrendipine.

Introduction

According to the World Health Organization, approximately 62% of cerebrovascular disease and 49% of ischemic heart disease are attributable to suboptimal blood pressure control. Worldwide, high blood pressure is estimated to cause 7.1 million deaths per year (i.e., 13% overall mortality) [1].

High blood pressure in nondiabetics is defined as a diastolic blood pressure (DBP) >90 mm Hg and/or a systolic blood pressure (SBP) >140 mm Hg and graded into mild (SBP 140–159 and/or DBP 90–99 mm Hg), moderate (160–179 and/or 100–109 mm Hg) and severe hypertension (≥180 and/or ≥110 mm Hg) [2].

The effectiveness of antihypertensive drug treatment is well established and has been quantified in terms of overall reduction in the relative risk for cerebrovascular events (such as stroke and transient ischemic attack) and cardiovascular diseases (such as myocardial infarction [MI] and angina pectoris [AP]) [3–9].

In patients with moderate to severe hypertension, without cardiovascular or cerebrovascular diseases (primary prevention population), there is evidence that the angiotensin receptor blocker (ARB) eprosartan (Teveten, Tevetens, Barcelona, Spain) is more effective in lowering SBP as directly compared to the angiotensin-converting-enzyme inhibitor (ACEI) enalapril [10]. During the past 10 years, several prospective cohort studies and meta-analyses have documented that SBP is a more important risk factor for cardiovascular (CV) and cerebrovascular (CBV) diseases than DBP, as was believed in the past [6,7,11–14].

In the field of secondary prevention the PROGRESS study (Perindopril Protection Against Recurrent Stroke Study) was the first large trial to document the positive influence of hypertension treatment on the CV and CBV risk within a population of patients with a primary CBV event. In this study, the ACEI perindopril (in possible combination with the diuretic indapamide) was compared to a placebo [15].

Further evidence for the reduction of CV and CBV events within a population of patients with previous CBV events (stroke and/ or transient ischemic attack [TIA]) was provided by the MOSES study (MOrbidity and mortality after Stroke—Eprosartan vs. nitrendipine for Secondary prevention). In this secondary prevention study, the calcium channel blocker (nitrendipine) was compared to the ARB eprosartan [16]. Although the blood pressure reduction in both study arms was comparable (as intended by the study protocol) eprosartan showed a significantly greater relative risk reduction for CV and CBV events and overall mortality compared to that of the patients treated with nitrendipine. It is likely that this effect is attributable to greater stimulation of the angiotensin II receptor and improved endothelial function (both not measured in MOSES) in patients on ARB therapy [17].

As both comparator substances, enalapril and nitrendipine, are available as generics depending on the country, there is a sizeable price difference between them and eprosartan. This

Address correspondence to: Birgit Gradl, Solvay Pharmaceuticals Marketing & Licensing AG; Hegenheimermattweg 127, CH-4123 Allschwil, Switzerland. E-mail: birgit.gradl@solvay.com

10.1111/j.1524-4733.2009.00507.x

Funding: Financial support for this study was provided entirely by a grant from the Solvay Pharmaceuticals GmbH.

poses the question of whether the improved ability to lower SBP with eprosartan in primary prevention, as well as the risk reduction in secondary prevention, translates into sufficient health gains in quality adjusted life years (QALYs) to justify the higher cost.

Methods

The HEALTH (Health Economic Assessment of Life with Teveten for Hypertension) model is an object-oriented probabilistic Monte Carlo simulation model based on a Markov process with first- and second-order calculations [18]. The model was developed using Delphi and C++ for the operating systems Windows 98, ME, 2000, and XP. The Borland Delphi development environment was used as the primary programming tool.

Markov Health States

The main Markov health states simulated by the model are "CV & CBV naive" (starting stage for the primary prevention population), "CV events," "CBV events" (starting stage for the secondary prevention population), and "Death." The "CV event" state is further classified in MI, AP, and other CV events and the "CBV event" state is further classified in stroke, TIA, and other CBV events. A simplified structure of the Markov approach is shown in Figure 1.

Health State Transition

The health-state transitions are calculated in a stepwise procedure and depend on the patient's CV and CBV risk profile and on the therapy effect. First, a base risk for CV and CBV events is calculated and combined with a relative risk reduction based on the SBP reduction. In the secondary prevention analysis, an additional risk reduction beyond blood pressure reduction is applied, based on the outcomes of the MOSES trial. These simulations steps are described in detail in the following including the mortality predictions and the randomization procedure used within the model.

Base risk assessment. The Framingham algorithms, which are published in detail elsewhere [19,20], were used to predict the base risk of specific CV and CBV events. For the prediction of CV events, the risk equation published by D'Agostino et al. was used [19]. The cardiovascular events included in the model were AP and MI. The risk equation published by Wolf et al. was used to predict the risk of the CBV events stroke and TIA [20]. Because of the fact that the Framingham risk equations cover several CV and CBV events, additional groups named "other CV events" and "other CBV events" were included in the model to account coronary insufficiency, intracerebral hemorrhage, and subarachnoid hemorrage.

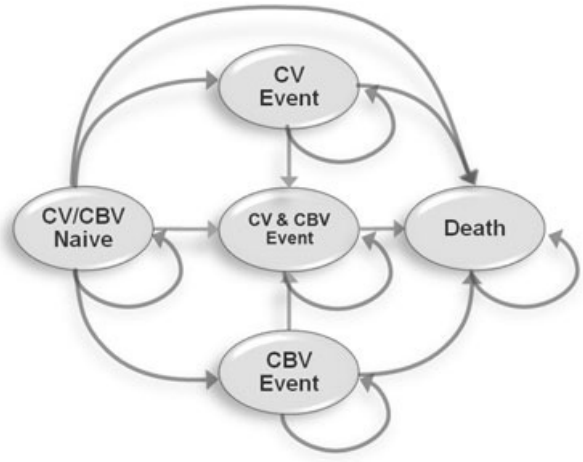

Figure 1 Simplified structure of the Markov approach.

For predicting the base risks in a population with previous CBV events (secondary prevention population), the Framingham algorithms were adjusted using the outcomes of the MOSES study [16]. The rationale for adjusting the Framingham algorithms was the greater power of the MOSES study in patients with previous CBV events and concomitant hypertension. In contrast to the Framingham population that included 216 patients with previous CBV events and concomitant hypertension [21], the MOSES study included 1352 patients.

Risk reduction related to the systolic blood pressure reduction. To estimate the effect of antihypertensive therapy on the risk reduction of CV and CBV outcomes, a systematic literature search was conducted.

The literature review revealed a meta-analysis conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration which provided all the necessary data on SBP-related risk reduction for a primary prevention population [7]. This meta-analysis by Turnbull et al. summarized data from 29 randomized controlled trials including a total of 162,341 patients. The duration of follow-up ranged from 2.0 to 8.4 years with a mean duration of around 5 years. This study concluded that the weighted mean SBP differences between randomized groups seemed to be directly associated with differences in risk of CV and CBV events. By contrast, differences in blood pressure were not associated with the risk of heart failure. Therefore, the HEALTH model focused on CV diseases (including MI and AP) and CBV diseases (including stroke and transient ischemic attack) as the primary clinical outcomes. On the basis of the combined data of all drug regimen comparisons provided in the meta-analysis, a regression analysis was performed to determine the connection between the relative risk reduction of CV and CBV events and systolic blood pressure reduction (SBPR). In both cases, an exponential function was the best estimate with an R^2 of 0.812 and a *P*-value of 0.002 for CV events [EXP (0.02886 × SBPR in mmHg [e.g., –10 mm Hg])] and a R^2 of 0.927 and a *P*-value of 0.0001 in for CBV events [EXP (0.06258 × SBPR in mmHg [e.g., –10 mm Hg])], respectively.

The relative risk reduction of CBV events for patients with a previous CBV event was calculated via the same methodology previously described based on data from a meta-analysis by Rashid et al. [6]. Also in this case, an exponential function was the best estimate with an R^2 of 0.872 and a *P*-value of 0.002 [EXP (0.03716 × SBPR in mmHg [e.g., –10])].

As data on the impact of lowering SBP on the secondary prevention of CV events (CV event risk in patients with a previous CV event) are scarce, the model assumed two extreme scenarios: the relative risk reduction for CV events would be 1) zero (worst scenario); or 2) equivalent to that calculated in the primary prevention regression analysis (best scenario). For the base case scenario, it is assumed that the relative risk reduction based on SBP is 50% of the reduction observed in primary prevention trials. Sensitivity analyses were employed to test the influence of the extreme cases (no risk reduction or the same risk reduction as in the primary prevention trials).

Risk reduction beyond blood pressure reduction. In the secondary prevention observation using the HEALTH model, an addi-

tional risk reduction beyond blood pressure reduction was modeled for patients with previous CBV events. These additional risk reductions of 25% for CV and of 25% for CBV events were applied to the eprosartan arm only on the basis of the results of the MOSES study [16].

Mortality. The probability of death after specific CV and CBV events was evaluated using the death rate prediction of the Framingham heart study published by Cupples et al. [22]. The general probability of death was estimated on the basis of country-specific life tables retrieved from the WHO website [23].

For the secondary prevention simulations, two different mortality settings were analyzed. In the base case setting, the probability of death was calculated on the basis of the Framingham mortality algorithms. In the sensitivity analyses, the mortality investigated in the MOSES study was simulated. This probability of death was lower than the probability predicted by the Framingham algorithms. The mean 1-year period from the occurrence of the CBV to the patient's recruitment in the MOSES study was identified as the main reason for this difference because mortality (especially mortality because of stroke) is highest in the first year after the event, according to published studies [24,25]. Hence, compared to a real-world scenario, the mortality observed in the MOSES study might have been underestimated because of the fact that some patients had already died during the 1-year period between the qualifying event and inclusion in the study.

Randomization and simulation. For the simulation of the occurrence of an event or mortality, the model used combined multiple recursive 64-bit random number generators to produce a uniformly distributed integer between 0 and 2^{377} with a periodicity = 3.0783e+113 [26]. Each patient had an individual random number generator enabling the simulation of events and mortality independent from other patients. Thus, each patient was regarded as an individual, to gain the best possible approximation to a real world scenario.

For the simulation of the occurrence of an event, a random number was drawn at each time step. If the random number was less than or equal to the transition probability for the current health state or parameter change, transition to the next health state occurred.

Time Horizon

A lifelong perspective was used. Therefore, the model discriminates between a treatment time horizon and a lifelong follow-up period.

The treatment time horizon used in the primary prevention base case analysis was set to 5 years based on the meta-analysis by Turnbull et al. that provided all necessary data concerning the CV and CBV event risk reduction. This treatment time horizon was varied in sensitivity analyses.

In the field of secondary prevention, a treatment time horizon of 2.5 years was selected based on the mean treatment period within the MOSES study.

For modeling the treatment follow-up effects after the treatment time horizon, it was assumed that treatment was stopped in all patients, thus neither treatment costs (drug and monitoring costs) nor treatment effects (blood pressure reduction; effect beyond blood pressure reduction) were simulated after the treatment time horizon.

SBP Reduction

In the field of primary prevention, a study by Sega et al. [10] was used as the basis for the SBPR of eprosartan and enalapril. This study compared the efficacy of eprosartan (n = 59) to that of enalapril (n = 59) in patients with moderate to severe hypertension. Sega et al. found a significant difference ($P = 0.025$) in SBP at the study end point when comparing the eprosartan (–29.1 ± 2.9 mm Hg) group to the enalapril (–21.1 ± 2.7 mm Hg) group.

In the case of secondary prevention for drugs, nitrendipine and eprosartan, the same blood pressure reduction was applied based on the results of the MOSES study. Because of the fact that the blood pressure reduction in MOSES was comparable between the nitrendipine and eprosartan arm, the mean systolic blood pressure reduction of 15.99 mmHg relating to the 671 patients of the Nitrendipine arm was taken into account [16]. This procedure is based on the fact that the adjustment of the Framingham algorithms to the MOSES outcomes was based on the Nitrendipine arm, where no risk reduction beyond blood pressure reduction was observed.

In the case of compliance to treatment, the blood pressure reduction of the RCTs was taken into account for each treatment strategy. In the case of noncompliance, the systolic blood pressure reduction was set to zero.

Patient Compliance

As the HEALTH model has a 5-year base case treatment time horizon for the primary prevention simulations and a 2.5-year treatment time horizon for the secondary prevention simulations, data from the Conlin et al. study were used to estimate persistence data over 5 years of drug treatment [27]. This study investigated the persistence pattern of a large, geographically diverse, drug-insured population of 15,175 patients over a 4-year period. According to this study, switch rates were comparable for all drug classes, except for thiazide diuretics, which showed a higher switch rate.

Because of the fact that the model investigates the efficacy of an ARB versus specific comparators and because it is not known to which drugs patients in these regimes would switch, switching has not been taken into account. The model differentiates between compliance and noncompliance only. Conlin and colleagues report 12-month persistence on ACEI of 60.7%, excluding a 9.6% switch rate. The following calculation was made to adjust for switching; $(60.7\% \times 1) \div (1 - 9.6\%) = 67.2\%$.

Thus, the compliance rates used for the primary prevention simulations in the model were: ARB 73.3% and 60.9% after the first and fourth years, respectively; ACEI 67.2% and 57.3% after the first and fourth years, respectively. Data on partial compliance (e.g., irregular drug use) for the drug classes ARB and ACEI were not identified; hence, this aspect was not included in the model.

Published compliance data for a secondary prevention (high-risk patients with previous CBV events and concomitant hypertension) population are very limited. According to one German study, the overall compliance rate for antihypertensive treatment 1 year after the stroke event was 90.8% [28]. Compared to the compliance rates within a primary prevention population after 1 year (ARB 73.3%, ACEI 67.2%, CCB 60.0%, and diuretics 48.6%) [27], this overall compliance rate (90.8%) was greater in the high-risk patients with previous stroke.

As a result of this difference, it seems to be impossible to define adequate compliance rates in the field of secondary prevention without applying major assumptions. Therefore, the analyses in the field of secondary prevention were performed without considering patient compliance (compliance was set to 100%).

Discounting

Future costs and health effects were discounted according to country-specific guidelines for health economic evaluations. The

Table 1 Country-specific discount rates used in the HEALTH model

Country	Discount rate		Reference
	Health effects	Costs	
Belgium	3.5%	3.5%	[29]
Germany	5.0%	5.0%	[30]
Norway	4.0%	4.0%	[31]
Spain	3.5%	3.5%	[32]
Sweden	3.0%	3.0%	[33]
United Kingdom	3.5%	3.5%	[34]

discount rates for health effects and costs used are shown in Table 1.

Willingness-to-Pay Threshold per QALY Gained

In the United Kingdom, the cost per QALY gained threshold assessed to be cost-effective is £20,000 [≈ €30,000], although recent reimbursement decisions made by the National Institute for Health and Clinical Excellence show that the upper limit is moving toward a cutoff point of £30,000 (≈ €45,000) [35].

The Swedish National Board of Health and Welfare discriminates between low (<SEK 100,000), moderate (SEK 100,000 to 500,000), high (SEK 500,000 to 1,000,000) and very high costs (>SEK 1,000,000) per QALY gained [36]. According to experienced health economists, costs per QALY gained within the low and moderate range are usually regarded as cost-effective [37,38], leading to a threshold of SEK 500,000 (≈ €54,000) per QALY gained.

In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG) gave an upper limit for the cost per QALY threshold of €50,000 in their first version method article [39]. Nevertheless, in newer method articles, the QALY method is put into question in general and no further statement on this threshold is given.

In all other countries investigated (Belgium, Spain, and Norway), there is no official information on the willingness to pay threshold per QALY gained.

To make the country results comparable to each other we generally applied the lower UK willingness to pay threshold of €30,000 as the cutoff value for cost-effectiveness, independent of possibly higher QALY thresholds in individual countries.

Input Data

Population Characteristics

To calculate the risk for CV and CBV events, specific population characteristics were used to apply the Framingham algorithms.

For the primary prevention population (patients without any CV or CBV event at baseline), country-specific population characteristics for hypertensive patients have been derived on the basis of published literature and/or by analyses of population health surveys. The population input data for the primary prevention simulations is shown in Table 2 for Belgium, Germany, and Norway and in Table 3 for Spain, Sweden and the United Kingdom.

For the secondary prevention population, the patient characteristics of the MOSES study population were applied for each country. The rationale for this procedure was the fact that country-specific data for this highly selective patient cohort (hypertensive patients with a previous CBV event) have not been identified. The population input parameters for the secondary prevention simulations are shown in Table 4.

Health Utility Weights

According to the health states achieved during the simulation process, different utilities were applied to each patient modeled based on published literature. Each patient started with a health utility value based on a typical hypertensive patient depending on sex and mean age. During the simulation process, the utility was reduced by an event-specific utility reduction factor if a specific CV or CBV event developed in the patient. If the patient died because of an event or because of other reasons, the health utility was set to zero.

The utility values applied to the model were based on a Swedish study [60]. In this study, data from the 1996–1997 Survey of Living Conditions (ULF), a cross-sectional study based on personal interviews with a representative sample (n = 11,698, aged 16–84) of the Swedish population were used. The health utility was evaluated by the EQ-5D self-classifier. The cohort included 869 patients with hypertension, 520 with ischemic heart disease and 86 with stroke.

Within the HEALTH model, the same utility values were applied for MI and AP (ICD-9 410–414) as well as for stroke and TIA (ICD-9 430–438) because of the fact that the population-

Table 2 Population characteristics—primary prevention setting (Belgium, Germany, and Norway)

Parameter	Belgium*			Germany			Norway†		
	Males	Females	Ref.	Males	Females	Ref.	Males	Females	Ref.
Proportion (males/females)	48%	52%	[40]‡	48%	52%	[40]‡	44%	56%	[41]
Age in years	57.3 (±12.0)	60.6 (±11.3)	[40]‡	57.3 (±12.0)	60.6 (±11.3)	[40]‡	64.3 (±11.3)	66.7 (±11.3)	[42]
Baseline SBP in mm Hg¶	179.2 (±2.3)	179.2 (±2.3)	[10]	179.2 (±2.3)	179.2 (±2.3)	[10]	179.2 (±2.3)	179.2 (±2.3)	[10]
Baseline DBP in mm Hg¶	116.8 (±0.5)	116.8 (±0.5)	[10]	116.8 (±0.5)	116.8 (±0.5)	[10]	116.8 (±0.5)	116.8 (±0.5)	[10]
Patients with diabetes	12.1%	13.4%	[40]‡	12.1%	13.4%	[40]‡	11.4%	12.0%	[41]
Current smoker	24.4%	12.6%	[40]‡	24.4%	12.6%	[40]‡	20.4%	15.4%	[42]
Left ventricular hypertrophy	17.5%	18.5%	[43]	17.5%	18.5%	[43]	14%	9%	[44–46]
Atrial fibrillation	1.6%	1.4%	[47]	1.6%	1.4%	[47]	3.1%	2.8%	[48]
Total cholesterol in mg/dl	247.2 (±47.3)	257.3 (±44.7)	[40]‡	247.2 (±47.3)	257.3 (±44.7)	[40]‡	239.4 (±42.5)	258.7 (±50.2)	[42]
HDL-cholesterol in mg/dl	49.6 (±15.2)	62.4 (±17.8)	[40]‡	49.6 (±15.2)	62.4 (±17.8)	[40]‡	46.3 (±15.4)	54.1 (±15.4)	[42]
Mean age at menopause#	—	52.0	[49]	—	52.0	[49]	—	49.0	[50]
Alcohol consumption**	—	31.0%	[40]‡	—	31.0%	[40]‡	—	65.3%	[51]

*Because of the fact that published literature lacks Belgian population characteristics, German data was applied.
†In cases where Norwegian data were not identified Swedish data were used as proxy.
‡Data are based on our own analysis of the German Federal health survey 1998.
¶Baseline blood pressure data was based on the Sega et al. study.
#During the simulation the mean age of menopause was used to simulate whether a female patient had already entered menopause.
**According to the Framingham algorithms moderate alcohol consumption has only a preventive effect in females.
SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 3 Population characteristics—primary prevention setting (Spain, Sweden, and the UK)

	Spain			Sweden			UK		
Parameter	Males	Females	Ref.	Males	Females	Ref.	Males	Females	Ref.
Proportion (males/females)	43%	57%	[52]	44%	56%	[53]	46%	54%	[54]*
Age in years	67.0 (±7.9)	68.2 (±8.2)	[52]	65.4 (±11.2)	66.9 (±11.7)	[53]	64.8 (±12.3)	67.2 (±12.6)	[54]*
SBP in mm Hg†	179.2 (±2.3)	179.2 (±2.3)	[10]	179.2 (±2.3)	179.2 (±2.3)	[10]	179.2 (±2.3)	179.2 (±2.3)	[10]
DBP in mm Hg†	116.8 (±0.5)	116.8 (±0.5)	[10]	116.8 (±0.5)	116.8 (±0.5)	[10]	116.8 (±0.5)	116.8 (±0.5)	[10]
Patients with diabetes	31.0%	30.0%	[52]	26.3%	19.2%	[53]	14.6%	10.8%	[54]*
Current smoker	30.7%	6.5%	[52]	15.0%	10.6%	[53]	13.7%	14.7%	[54]*
Left ventricular hypertrophy	23.4%	17.8%	[52]	14%	9%	[44]	10.2%	6.2%	[54]*
Atrial fibrillation	7.9%	8.0%	[52]	3.1%	2.8%	[48]	4.5%	3.7%	[54]*
Total cholesterol in mg/dl	219.2 (37.5)	219.2 (37.5)	[52]	222.9 (±41.5)	244.8 (±47.0)	[55]	211.8 (±44.2)	235.3 (±47.0)	[54]*
HDL-cholesterol in mg/dl	56.4 (20.9)	56.4 (20.9)	[52]	38.2 (±9.2)	44.6 (±9.8)	[55]	51.8 (±14.3)	61.9 (±15.6)	[54]*
Mean age at menopause‡	—	50.0	[56]	—	51.3	[57]	—	51.0	[54]*
Alcohol consumption§	—	20.0%	[58]	—	65.3%	[51]	—	58.7%	[54]*

*Data are based on our own analysis of the England health survey 2003.
†Baseline blood pressure data was based on the Sega et al. study.
‡During the simulation the mean age of menopause was used in order simulate whether a female patient had already entered menopause.
§According to the Framingham algorithms moderate alcohol consumption has only a preventive effect in females.
SBP, systolic blood pressure; DBP, diastolic blood pressure.

based Swedish study on health utility weights used this combined disease classification.

In view of the fact that additionally a secondary prevention population was simulated, a differentiation between a utility reduction for the first event and a utility reduction for the subsequent events was made.

By reviewing data from an overview of preference weights, a general convention was identified. According to the overview of published health utilities, the utility reduction for subsequent CV and CBV events is half of the utility reduction of the primary event [61].

The health utility weights used in the model are shown in Table 5. To calculate a population's baseline utility value, the basis utility was adapted by the age-specific utility summand using the population's mean age at baseline and reduced by the utility reduction for hypertension. An age-related utility adaptation during the simulation process was not applied, thus sensitive analyses, simulating the lowest possible age-related baseline utility (basis utility minus utility reduction for hypertension; males = 0.685; females = 0.6443) and the highest possible age-related baseline utility (basis utility – utility reduction hypertension + x for 20–29-year-old subjects; males = 0.9052; females = 0.8645) were applied.

Additionally, a 10% variation of the baseline utility and the disutilities has been simulated to investigate possible country-specific variations of the EQ-5D health utility weights.

Cost Data

An overview of the therapy costs and of the cardiovascular and cerebrovascular event costs used in the model is given in Table 6.

Drug costs are based on defined daily doses (DDD) of each medication; hence, the costs of 600 mg eprosartan, 10 mg enalapril, and 20 mg nitrendipine were used in the model. Nitrendipine is not licensed in Norway, Sweden, and the UK. In this case, the costs of another frequently used calcium channel blocker, amlodipine 5 mg, were applied. The drug costs are based on an average price calculated over the DDD of all reimbursed products of the same substance within a country.

Table 4 Population characteristics—secondary prevention setting

Parameter	Males	Females	Ref.
Proportion (males/females)	54.8%	45.2%	[16]*
Age in years	66.96 (±8.82)*	70.49 (±9.9)*	[16]*
SBP in mm Hg	152.47 (±18.66)	151.49 (±17.71)	[16]*
DBP in mm Hg	87.83 (±9.38)	86.44 (±9.77)	[16]*
Patients with diabetes	39.1%	36.0%	[16]*
Current smoker	26.4%	12.2%	[16]*
Left ventricular hypertrophy	5.7%	9.9%	[16]*
Atrial fibrillation	4.6%	7.6%	[16]*
Total cholesterol in mg/dl	247.2 (±47.3)	257.3 (±44.7)	[40]†
HDL-cholesterol in mg/dl	49.6 (±15.2)	62.4 (±17.8)	[40]†
Mean age at menopause‡	—	52	[59]
Alcohol consumption§	—	23.4%	[16]*
Previous myocardial infarction	10.1%	4.9%	[16]*
Previous angina pectoris	10.2%	9.8%	[49]
Previous other CV events	26.1%	28.7%	[16]*
Previous stroke	64.4%	56.1%	[16]*
Previous TIA	22.3%	33.7%	[16]*
Previous other CBV events	13.3%	10.2%	[16]*

*Data for males and females as well as parameters not shown in the MOSES publication have been provided on request by the MOSES study team.
†Cholesterol values have not been recorded during the MOSES study, thus data from the German federal health survey 1998 were used.
‡During the simulation the mean age of menopause was used to simulate whether a female patient had already entered menopause.
§According to the Framingham algorithms moderate alcohol consumption has only a preventive effect in females.
SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack.

Table 5 Health utility weights used in the HEALTH model

Health state	Males	Females
Basis utility	0.7257	0.6850
Utility adaptation because of age*	+X*	
Utility reduction hypertension†	−0.0407	
Utility reduction MI or AP primary event	−0.1156	
Utility reduction MI or AP subsequent event	−0.0578	
Utility reduction stroke or TIA primary event	−0.2743	
Utility reduction stroke or TIA subsequent event	−0.1372	

*X = 0.2202 (20–29 years); 0.2104 (30–39); 0.1897 (40–49); 0.1624 (50–59); 0.1335 (60–69); 0.0967 (70–79).
†Applied to all patients.
MI, myocardial infarction; AP, angina pectoris; TIA, transient ischemic attack.

Because of the fact that the model discriminates between compliance and noncompliance, the costs for therapy-related monitoring were included additionally.

For each event, country-specific direct health-care costs for the first year (after the occurrence of the event) as well as for the subsequent years (second and following years after occurrence of the event) were evaluated on the basis of published literature. If more than one cost value was identified for the same event, a mean value was calculated. The cost data used reflects a health-care payer perspective.

All cost values retrieved from published literature were inflated to 2007 values using the country-specific health-care cost indexes (Belgium [62], Germany [63], Norway [64], Spain [65], Sweden [66], and the UK [67]).

Because of a lack of published literature, the Norwegian event costs have been estimated on the basis of Swedish event cost data using a Norwegian study [68] on stroke costs as the transformation basis. According to the comparison of Swedish and Norwegian costs for stroke care the Norwegian health-care costs are around 6% higher than the Swedish health-care costs, hence the Norwegian health-care costs are estimated using this transition factor.

All costs were transferred to euros using the average exchange rate of the year 2007 (January to November) provided by the European Central Bank [69].

Analyses

Analyses were performed using patient cohorts of 1000 patients and 1000 iterations (different starting numbers of the random number generator) for each cohort using a 5-year treatment time horizon in primary prevention and a 2.5-year treatment time horizon in secondary prevention, simulating the treatment follow-up effects over lifetime. The incremental cost-effectiveness ratio (ICER) is shown as mean costs per QALY gained from a health-care payer perspective.

A probabilistic sensitivity analysis was performed to show the variability of results based on randomization (first order) and input parameter distributions (second order).

The influence of changes in single parameters was tested in one-way sensitivity analyses that are shown as a tornado diagram.

In the field of primary prevention, this includes the discounting of costs (0–10%) and effects (0–10%), the secondary prevention of CV diseases (no RR reduction; RR risk reduction = primary prevention), systolic blood pressure reduction (extreme cases using the upper and lower confidence intervals); the treatment time horizon (1 year and 10 years), the utility reduction caused by TIA (reduction was set to zero), the baseline utility

Table 6 Overview of cost data used in the HEALTH model—costs are given in the Euro values of 2007

	Belgium		Germany		Norway		Spain		Sweden		UK	
Cost unit	Costs (€)	Ref.	Costs (€)	Ref.	Costs (€)	Ref.	Costs (€)	Ref.	Costs (€)	Ref.	Costs (€)	Ref.
Eprosartan 600 mg/day	0.88	[70]	1.16	[71]	0.90	[72]	0.55	[73]	0.86	[74]	0.75	[75]
Enalapril 10 mg/day	0.21	[70]	0.29	[71]	0.19	[72]	0.09	[73]	0.16	[74]	0.03	[75]
Nitrendipine 20 mg/day	0.83	[70]	0.32	[71]	0.41*	[72]	0.41	[73]	0.34*	[74]	0.07*	[75]
Yearly monitoring costs	209	[76]	126†	[77]	232	[68,78]	173‡	[79]	219	[78]	188‡	[80]
Stroke 1st year	15,648	[81–83]	17,629	[84–87]	21,351	[68]	8,066	[79,81,85,86,88]	20,153	[78,81,89,90]	14,028	[91,92]
Stoke subsequent years	3,533	[81,82]	7,337	[84,86]	8,616	[68,78,93]	3,368	[79,81,86]	8,133	[78,93]	3,633	[91,92]
TIA 1st year	2,175§	[94,95]	3,365	[96,97]	2,266	[98]	2,079	[99]	1,669	[100,101]	1,737	[80,102]
TIA subsequent years	0		0		0		0		0		0	
MI 1st year	8,503	[81,82,103]	11,683	[85,86,104,105]	13,552	[68,78,81,93]	10,988	[79,81,85,105]	12,791	[78,81,93]	9,906	[102,106]
MI subsequent years	1,287	[103]	2,803	[86,104]	2,490	[68,78,81]	3,087	[79,81]	2,350	[78,81]	2,958	[81,106]
AP 1st year	6,990	[82,103]	4,153	[86,104,107]	6,986	[68,78,93]	2,286	[86,108]	6,594	[78,93]	5,405	[102,106]
AP subsequent years	1,132	[82,103]	1,315	[86,104,107]	1,413	[68,78]	483‖	[108]	1,333	[78]	2,072	[106]

TIA, transient ischemic attack; MI, myocardial infarction; AP, angina pectoris.
*Nitrendipine is not licensed in Norway, Sweden and the UK, hence the costs of amlodipine (5 mg) were used as model input.
†GP ordination complex (50% EBM #03111 plus 50% EBM #03112) plus consultation, discussion and/or clarification (EBM #03120) plus therapy and care of a patient with a chronic internal condition (EBM #03210) assuming four visits per year and an EBM point value of €0.04 using the EBM version of the fourth quarter 2007.
‡Assumption: four visits to the health centre per year.
§Cost per day €282 [94]—estimation mean length of stay 7.7 days (based on German data [97]).
‖Estimation on the basis of the mean relation of the first AP year cost to the subsequent year AP cost of the other 5 countries; exchange rates used: 1 Euro = 0.6811 British Pounds; 1 Euro = 9.234 Swedish Krona; 1 Euro = 8.031 Norwegian Krona.

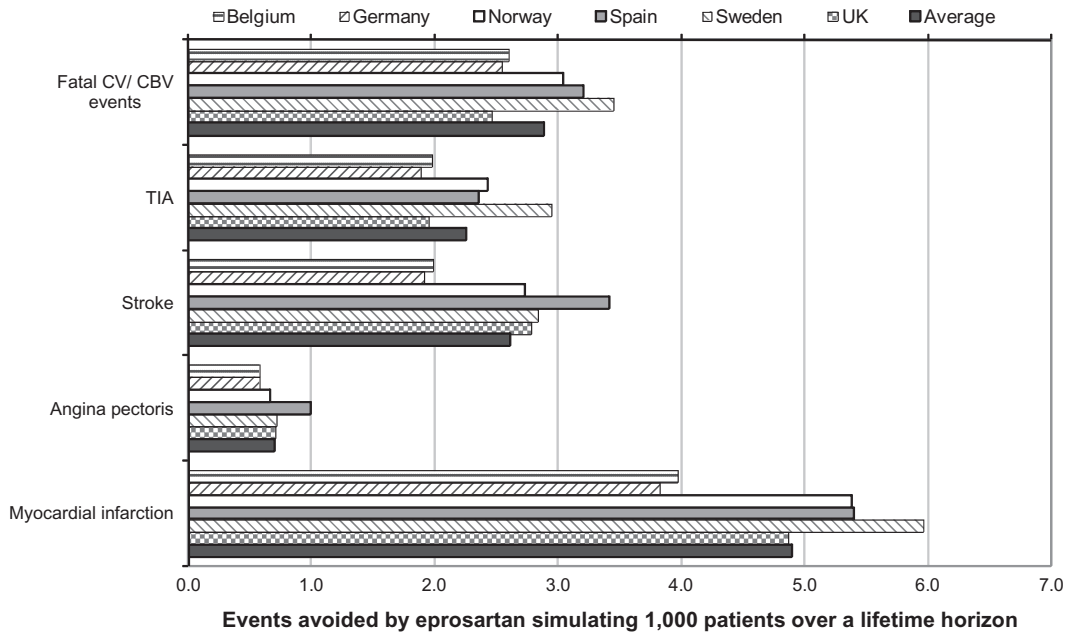

Figure 2 Events additionally avoided by eprosartan compared to enalapril in 1000 patients simulating a lifetime horizon (primary prevention).

according to age (minimum and maximum values), the variation of health utility weights by ±10% and the effect of excluding patient compliance on ACEIs and ARBs (setting year 1 and year 4 compliance to 100% for both primary treatments).

Furthermore, the variations in the cost-effectiveness were tested using different population characteristics that were assumed to have a major influence on the basic risk for CV and CBV events. Therefore, analyses were performed for males (100%) and females (100%), different age groups and patients with and without type 2 diabetes.

In the field of secondary prevention, the one-way sensitivity analyses focus on the discounting of costs (0–10%) and effects (0–10%), the secondary prevention of CV diseases (no RR reduction; RR risk reduction = primary prevention), blood pressure reduction beyond blood pressure reduction for CV events (reduction was set to zero); the treatment time horizon (1 year to 10 years), the utility reduction caused by TIA (reduction was set to zero), the baseline utility according to age (minimum and maximum values) the variation of health utility weights by ±10%.

Furthermore, the variations in the cost-effectiveness were tested using different population characteristics that were assumed to have a major influence on the basic risk for CV and CBV events. Therefore, analyses were performed for males (100%) and females (100%), different age groups and patients with and without type 2 diabetes.

The ICER scatter-plots as well as the tornado diagrams are shown for those countries that represent the lowest and the highest mean cost per QALY gained within a primary prevention and a secondary prevention population, respectively. The rationale for this procedure is that only four scatter-plots and tornado diagrams have to be presented (instead of 16) and that this procedure enables the extreme variations of the modeling results to be presented by choosing the countries with the extreme results (highest and the lowest mean ICER per QALY gained).

Results

Primary Prevention

Within a primary prevention cohort of 1000 patients, simulating a lifetime horizon (treatment time horizon = 5 years), eprosartan therapy avoided on average 2.9 MIs, 2.3 AP cases, 2.6 strokes, 0.7 TIAs, and 4.9 CV/ CBV mortality cases more than enalapril. The results of a primary prevention population in all countries are shown in Figure 2.

The mean costs per QALY gained in the primary prevention simulations, comparing eprosartan to enalapril, are shown in Table 7 and range from €7918 in Spain to €24,036 in Germany, simulating 1000 patients and 1000 iterations over a lifetime horizon. The undiscounted modeling results are given in brackets, to provide an estimate on the influence of the country-specific discount rates applied.

Secondary Prevention

Within a secondary prevention cohort of 1000 patients, simulating a lifetime horizon (treatment time horizon = 2.5 years), eprosartan therapy avoided on average 4.8 MIs, 7.0 AP cases, 9.4 strokes, 18.1 TIAs and 1.6 CV/CBV mortality cases more than nitrendipine. The results of a secondary prevention population in all countries are shown in Figure 3.

The mean costs per QALY gained in the secondary prevention simulations, comparing eprosartan to nitrendipine, are shown in Table 8 and range from €–5767 in Belgium to €9136 in Germany, simulating 1000 patients and 1000 iterations over a lifetime horizon. The undiscounted modeling results are given in brackets, to provide an estimate on the influence of the country-specific discount rates applied.

Probabilistic Sensitivity Analyses

The incremental cost-effectiveness scatterplots for the extreme scenarios in primary (Spain and Germany) and secondary

Table 7 Costs, utilities and cost per QALY gained comparing eprosartan to enalapril in primary prevention (1000 patients & 1000 iterations)

	Eprosartan		Enalapril		Incremental		
Country	Costs (€)	Utilities	Costs (€)	Utilities	Costs (€)	Utilities	ICER (€) per QALY
Belgium	6,277,551	10,359.0	5,629,136	10,322.7	648,415	36.3	17,863
	(9,711,995)	(15,181.2)	(9,022,023)	(15,123.6)	(689,972)	(57.6)	(11,979)
Germany	7,041,011	9,182.6	6,267,037	9,150.4	773,974	32.2	24,036
	(13,264,824)	(15,431.2)	(12,432,230)	(15,370.5)	(832,594)	(60.7)	(13,717)
Norway	8,123,926	8,456.1	7,566,432	8,415.8	557,494	40.3	13,834
	(12,649,227)	(12,247.0)	(12,055,162)	(12,183.7)	(594,065)	(63.3)	(9,385)
Spain	4,969,228	8,270.8	4,593,935	8,223.4	375,293	47.4	7,918
	(6,947,761)	(11,122.5)	(6,549,422)	(11,054.9)	(398,339)	(67.6)	(5,893)
Sweden	8,625,087	8,870.4	8,081,451	8,823.9	543,636	46.5	11,691
	(12,071,172	(11,752.8)	(11,499,298)	(11,687.8)	(571,874)	(65.0)	(8,798)
UK	5,490,508	8,708.6	4,894,846	8,672.2	595,662	36.4	16,364
	(8,112,946)	(12,221.0)	(7,482,392)	(12,167.2)	(630,554)	(53.8)	(11,720)

ICER per QALY, Incremental cost-effectiveness ratio per QALY gained; cost and effects were discounted according to country-specific guidelines; (undiscounted modeling results are given in brackets).

prevention (Belgium and Germany) simulations are shown in Figure 4.

Considering a willingness to pay threshold of €30,000 per QALY gained the probability of eprosartan being cost-effective compared to enalapril was 61.2% in Belgium, 55.9% in Germany, 69.5% in Norway, 76.6% in Spain, 72.3% in Sweden and 63.5% in the UK, simulating a primary prevention population.

In secondary prevention, the probability that eprosartan is cost-effective compared to nitrendipine was 100%, independent of the country and considering €30,000 as the willingness to pay threshold.

One Way Sensitivity Analyses

The tornado diagrams for the primary prevention and the secondary prevention settings are shown in Figure 5.

In the primary prevention setting, the variables with the greatest influence on the analysis results were the patients' baseline age, systolic blood pressure reduction, the cost and effect discount rate, the patient's sex and the baseline systolic blood pressure. Considering the country simulation with the highest mean incremental cost-effectiveness ratio (Germany) the variation of these parameters led to mean costs per QALY gained that exceed the applied willingness to pay threshold of €30,000. Setting patient compliance rates for years 1 and 4 to 100% for both ACEI and ARB therapies also resulted in an ICER greater than €30,000 per QALY gained in Germany (€33,210 per QALY gained).

Because of the fact that the baseline age and the baseline systolic blood pressure could be influenced by the physician's patient selection for eprosartan therapy the cutoff values for cost-effectiveness have been investigated for all countries.

Starting from an age of 37 in Spain (ICER per QALY gained = €28,488) and from an age of 52 in Germany (ICER per QALY gained = €29,924) the therapy of eprosartan is cost-effective compared to enalapril, whereas in younger patients the willing-

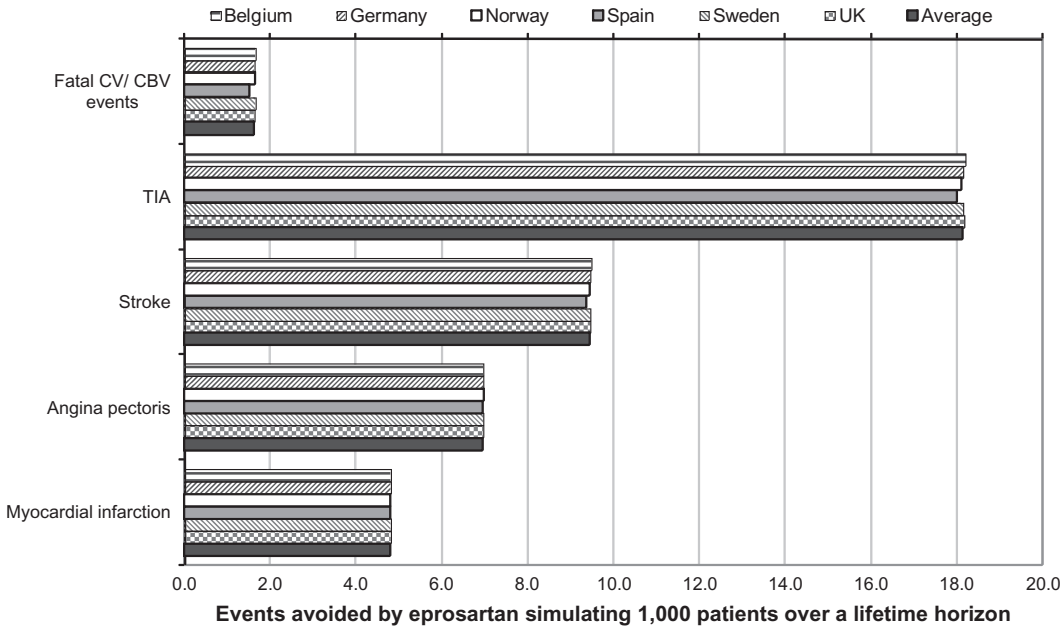

Figure 3 Events additionally avoided by eprosartan compared to nitrendipine in 1000 patients simulating a lifetime horizon (secondary prevention).

Table 8 Costs, utilities and cost per QALY gained comparing eprosartan to nitrendipine in secondary prevention (1000 patients & 1000 iterations)

	Eprosartan		Nitrendipine		Incremental		
Country	Costs (€)	Utilities	Costs (€)	Utilities	Costs (€)	Utilities	ICER (€) per QALY
Belgium	17,867,996	3,244.3	18,081,950	3,207.2	−213,954	37.1	−5,767
	(21,388,173)	(3,986.2)	(21,587,048)	(3,943.3)	(−198,875)	(42.9)	(−4,635)
Germany	28,967,343	3,041.8	28,643,914	3,006.4	323,429	35.4	9,136
	(36,813,615)	(4,037.1)	(36,440,516)	(3,993.7)	(373,099)	(43.4)	(8,597)
Norway	34,993,752	3,247.1	34,930,873*	3,210.0	62,879	37.1	1,695
	(42,658,337)	(4,114.9)	(42,555,073)	(4,071.0)	(103,264)	(43.9)	(2,352)
Spain	15,015,775	3,084.8	15,089,497	3,048.9	−73,722	35.9	−2,054
	(19,155,946)	(4,121.5)	(19,215,025)	(4,077.4)	(−59,079)	(44.1)	(−1,340)
Sweden	36,318,567	3,404.9	36,283,665*	3,366.4	34,902	38.5	907
	(42,422,941)	(4,085.6)	(42,352,811)	(4,041.8)	(70,130)	(43.8)	(1,601)
UK	19,313,238	3,292.4	19,087,933*	3,254.9	225,305	37.5	6,008
	(23,163,526)	(4,057.4)	(22,918,206)	(4,013.9)	(245,320)	(43.5)	(5,640)

*Nitrendipine is not licensed in Norway, Sweden and the UK, hence the costs of amlodipine (5 mg) were used as model input.
ICER per QALY, Incremental cost-effectiveness ratio per QALY gained; cost and effects were discounted according to country-specific guidelines; (undiscounted modeling results are given in brackets).

ness to pay threshold is exceeded. The exclusion of the patient compliance factor in Spain did not result in an ICER greater than the willingness to pay threshold (€10,734 per QALY gained).

The cutoff values for the baseline systolic blood pressure are 164 mm Hg (ICER per QALY gained = €29,694) in Germany whereas in Spain even patients within a mild systolic hypertension range (140–159 mmHg) showed excellent CE results (<€20,000 per QALY gained).

Within a secondary prevention setting, the patient's sex and baseline age had the most significant effect on cost-effectiveness results. These results, however, were still below the willingness to pay threshold of €30,000 even for the extreme case of Germany.

Discussion

Primary Prevention Setting

Simulating a health-care payer perspective over a lifetime horizon, the mean ICER per QALY gained by eprosartan in comparison to enalapril, was always below the assumed willingness to pay threshold of €30,000, independent of the country analyzed.

The highest costs per QALY gained have been observed simulating a German health-care setting (€24,036) followed by Belgium (€17,863), the UK (€16,364), Norway (€13,834), Sweden (€11,691) and Spain (€7918).

These results were extensively tested by sensitivity analyses that considered the analysis setting with the highest ICER per QALY gained, the German health-care setting, had a strong influence on the cost-effectiveness when applying a conservatively chosen cost per QALY gained threshold of €30,000.

The ICER was most sensitive to variations of the mean age at baseline, systolic blood pressure reduction, the cost and effect discount rate, the patient's sex, baseline blood pressure and patient compliance.

The influence of age on the cost-effectiveness of antihypertensives is well established [109]. Younger patients are in general at lower risk of experiencing CV and CBV events than older ones, thus a higher ICER is expected in younger patients from a health-care payer perspective. Considering the worst-case scenario (Germany) the cutoff age for cost-effectiveness, choosing a threshold of €30,000, was determined at 52 years of age. In younger patients the willingness to pay threshold was exceeded. Considering the best-case scenario (Spain) the cutoff age for cost-effectiveness was observed at 37 years of age. The cutoff ages within all other countries have not been investigated, but are expected to be located somewhere between the range of 37 and 52 years, observed in the two extreme scenarios.

In the model, systolic blood pressure reduction was used to estimate the preventive effect of antihypertensive drugs on CV and CBV events. The use of this approach has been confirmed by findings of recently conducted meta-analyses [6,7].

Modeling the extreme case using the upper 95% CI for enalapril and the lower 95% CI for eprosartan resulted in an ICER of eprosartan that exceeded €30,000 compared to enalapril. This extreme case of the 95% CIs, and so the lowest possible blood pressure reduction difference between eprosartan and enalapril, has to be regarded as a result that is statistically possible in individual patients but not in a whole population, where a blood pressure reduction near to the mean is to be expected. Nevertheless, this sensitivity analysis showed that the model is sensitive to variations in systolic blood pressure reduction.

Discounting future health effects and future costs has had a strong influence on the cost-effectiveness results. This is mainly based on the fact that a lifetime horizon was simulated and as a result most of the costs and health effects are to be expected in the future, which makes the results more sensitive to discounting in contrast to simulations focusing to a shorter observation period.

The influence of sex on the cost-effectiveness of antihypertensive treatments has already been investigated by a Scandinavian CE analysis [109]. In females the ICER per QALY gained was higher than in males. This variation is based mainly on the lower CV and CBV risk of females in comparison to males. This is confirmed with the general rule for preventive therapies (e.g., antihypertensive therapy) that says the lower the CV and CBV base risk, the lower the effect of a preventive therapy.

Sensitivity analyses varying the systolic baseline blood pressure values have shown a higher ICER per QALY gained the lower the baseline systolic blood pressure was. Considering the worst-case scenario (Germany) the cutoff value for cost-effectiveness was a baseline systolic blood pressure of 164 mm Hg. Starting from this blood pressure level cost-effectiveness was also achieved for a German health-care setting. In Spain the modeling results were not sensitive to the baseline systolic blood pressure.

The efficacy data used in the HEALTH model are mainly based on the Sega et al. study [10] that found a significant difference in systolic blood pressure reduction when comparing eprosartan to enalapril. The time horizon of this trial (10 weeks) does not deliver valid data for a 5-year treatment time horizon. Nevertheless, another study with a treatment duration of 2 years showed that eprosartan would keep the initial blood pressure

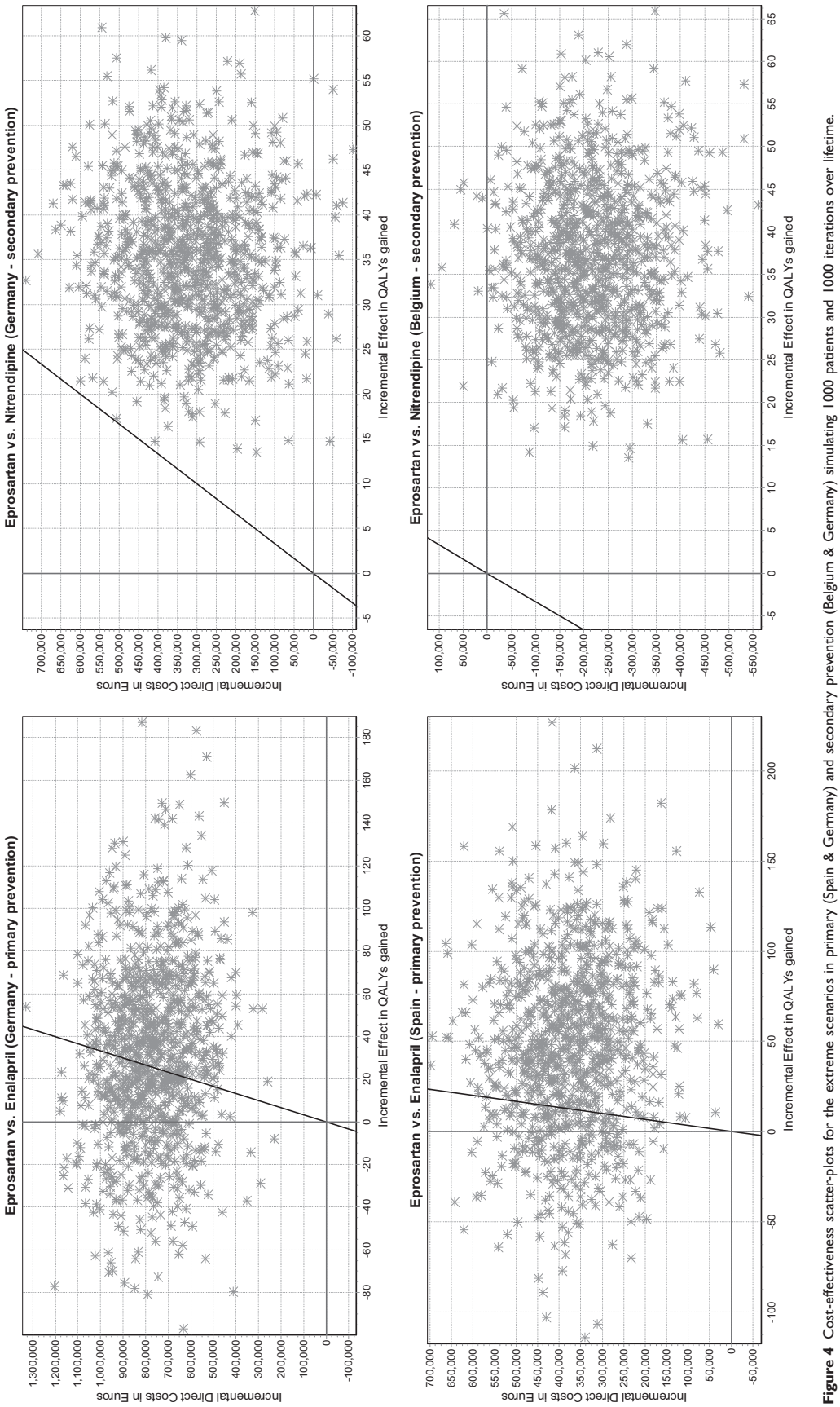

Figure 4 Cost-effectiveness scatter-plots for the extreme scenarios in primary (Spain & Germany) and secondary prevention (Belgium & Germany) simulating 1000 patients and 1000 iterations over lifetime.

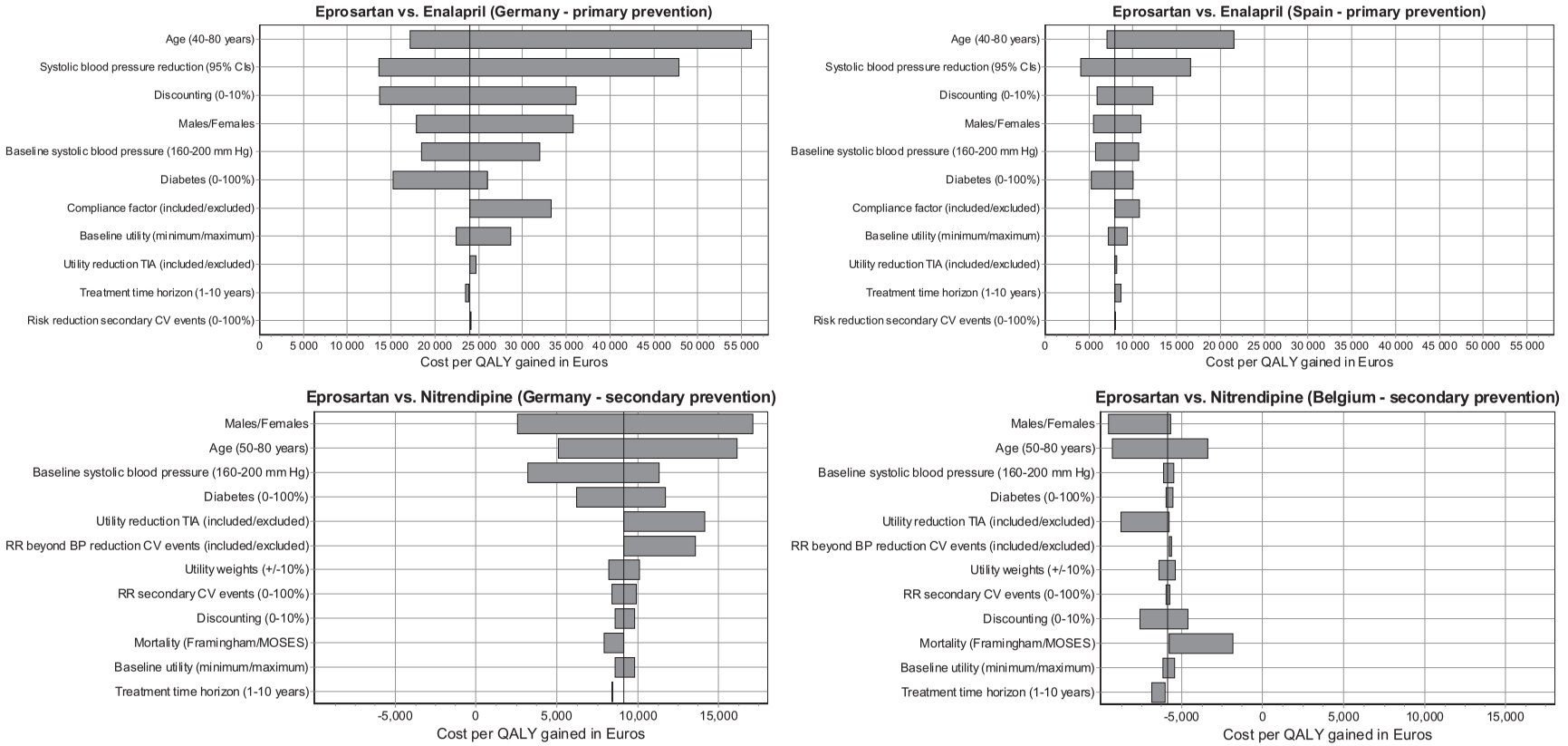

Figure 5 Tornado diagrams for the extreme scenarios in primary (Germany & Spain) and secondary prevention (Germany & Belgium) simulating 1000 patients and 1000 iterations over lifetime.

reduction at the titration end point (week 15) over the whole study period (2 years) [110]. According to this trial it is assumed that both eprosartan and enalapril will be able to maintain the initial blood pressure reduction over a long time horizon. Changes in systolic blood pressure reduction over this time horizon are taken into account by including the patient compliance that decreases continuously in the course of time [27]. Thus, the mean systolic blood pressure in each treatment arm rises continuously because of the fact that noncompliant patients were considered to have no blood pressure reduction. To test the influence of the treatment time horizon on the cost-effectiveness of eprosartan, sensitivity analyses assuming shorter and longer treatment time horizons were performed (1 year and 10 years) without showing a major impact on the cost-effectiveness of eprosartan.

The model uses the DDD costs of eprosartan and enalapril instead of the drug dose distribution observed in the Sega et al. trial. The rationale for this was that the twice-daily 400 mg eprosartan dose, as given to some patients within the underlying efficacy trial, is not available in all the countries investigated. If it were possible to reflect the drug doses used in the Sega study, a mean 683 mg daily dose of eprosartan (instead of 600 mg) would have to be compared to a mean 32.6 mg daily dose of enalapril (instead of 10 mg).

Thus, in general, using the DDD in the primary prevention setting is likely to underestimate the drug costs of enalapril, leading to a conservative estimation of the treatment cost of the comparators.

Secondary Prevention Setting

Simulating a health-care payer perspective over a lifetime horizon the mean ICERs per QALY gained by eprosartan in comparison to nitrendipine were always below the assumed willingness to pay threshold of €30,000, independent of the country analysed.

The highest costs per QALY gained have been observed simulating a German health-care setting (€9136) followed by the UK (€6008), Norway (€1695), Sweden (€907), Spain (€–2054), and Belgium (€–5767).

These results were extensively tested by sensitivity analyses. The ICER was most sensitive with respect to the baseline age as well as the sex, without changing the cost-effectiveness results fundamentally (all results remained below the assumed willingness to pay threshold of €30,000 per QALY gained). Both of these aspects (influence of age and influence of sex) have already been discussed in the previous chapter (primary prevention discussion).

The outcomes of the secondary prevention simulations are further strengthened by the results of the probabilistic sensitivity analyses that have shown convincing results with a probability of 100% that eprosartan is a cost-effective treatment strategy compared to nitrendipine regardless of the country analysed.

One limitation of the secondary prevention model, which is mainly based on the outcomes of the MOSES study, is the uncertainty concerning the mortality prediction in this specific population with stroke and concomitant hypertension. Therefore two different settings were analysed. In the first setting (base case) the probability of death was simulated by the Framingham mortality algorithms, whereas in the sensitivity analysis the MOSES mortality was applied. This probability of death based on the MOSES study was lower than the probability of death predicted by the Framingham algorithms. The mean 1-year period from the occurrence of the CBV to the patient's recruitment in the MOSES study was identified as the main reason for this difference, because mortality (especially mortality because of stroke) is highest in the first year after the event, according to published studies [24,25]. Simulating both approaches the Framingham mortality was considered to be more realistic and was therefore used for the base case analyses. Although there is the above mentioned uncertainty concerning the mortality prediction in the secondary prevention population, the impact of using the MOSES or the Framingham prediction on the cost per QALY gained is limited, as shown in the one-way sensitivity analyses.

Another limitation of the simulation was that we applied a risk reduction beyond blood pressure reduction for both CV and CBV events. Looking at the results of the MOSES study [16] there was a significant difference in the reduction of CBV and first CV events ($P = 0.026$ and $P = 0.03$) between the treatment groups, whereas the difference in reducing the recurrent CV events was only of borderline significance ($P = 0.061$). A further limitation of the secondary prevention analyses is that costs for nitrendipine were not available for Sweden, Norway and the United Kingdom. As a proxy, the local cost for amlodipine was used in each setting. This assumption may have improved cost-effectiveness claims for eprosartan if nitrendipine would be cheaper than amlodipine in these settings.

In view of the sizable difference in the number of CV events comparing eprosartan (4.95 CV events per 100 patient years) and nitrendipine (6.62 events per 100 patient years) we decided to simulate the CV risk reduction of 25% in the base case setting, although the statistical evidence only supports this procedure with respect to the first CV events, rather than with respect to recurrent CV events.

To investigate the impact of including the CV event risk reduction one way-sensitivity analyses have been performed that excluded the risk reduction for CV events beyond blood pressure reduction. The sensitivity analyses results show that the impact of excluding the CV event risk reduction had only a minor impact on the results without influencing the cost-effectiveness of eprosartan fundamentally.

We did not assess the benefits of fixed-dose combination therapies for hypertension in this analysis. A recent literature review has suggested that combination therapy may result in superior blood pressure reductions compared to monotherapy in hypertension [111]. Furthermore, recent clinical trials have suggested benefits for fixed-dose combination with an ARB and a calcium channel blocker because of superior blood pressure reduction and better tolerability than either agent alone [112]. Nevertheless, the combination of telmisartan and ramipril in the recent ONTARGET trial was not shown to improve survival or reduce renal events in patients with mild hypertension [113], and guidelines for the treatment of hypertension in the United Kingdom stipulate that combination therapy should be used only when patients fail to reach blood pressure targets on monotherapy [114]. Given conflicting evidence on the benefits of combination therapy for primary prevention, our findings that eprosartan as monotherapy is a cost-effective alternative to enalapril are relevant.

Conclusion

The results of the HEALTH model simulations in Belgium, Germany, Norway, Spain, Sweden, and the UK provide evidence that eprosartan is a cost-effective treatment strategy compared to enalapril in primary prevention and to nitrendipine in secondary prevention.

The cost-effectiveness in primary prevention is especially sensitive to changes in central patient characteristics, such as age and baseline systolic blood pressure. These patient characteristics are the two main factors to be considered for the prescription of

eprosartan in primary prevention. Considering the country with the highest cost per QALY gained (Germany), starting from the age of 52 years and a baseline systolic blood pressure ≥164 mm Hg, eprosartan becomes a cost-effective treatment option compared to enalapril, although the generic price level leads to a sizable difference in the drug therapy costs, and the exclusion of patient compliance with treatment (both ACEI and ARB) did not result in cost-effectiveness in Germany. In all other countries analysed cost-effectiveness is also observed in younger patients and in patients with a lower baseline systolic blood pressure. Nevertheless, the focusing on older patients (≥50 years of age) with a higher systolic blood pressure (≥160 mm Hg) was identified as reasonable patient selection criteria to ensure a cost-effective application of eprosartan within a primary prevention setting.

The cost-effectiveness outcomes show considerable evidence for the cost-effectiveness of eprosartan compared to nitrendipine within a secondary prevention population in all countries investigated, without any limitation related to the patient selection.

Supporting information for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

References

1 Elliott P, Law M, Lawes C, et al. Quantifying Selected Major Risks To Health—High Blood Pressure, Murray C, Lopez A, The World Health Report 2002—Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization, 2002.

2 Mancia G, De Backer G, Dominiczak A, et al. ESH-ESC Guidelines for the management of arterial Hypertension: the task force for the management of arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16:135–232.

3 Pearce KA, Furberg CD, Rushing J. Does antihypertensive treatment of the elderly prevent cardiovascular events or prolong life? A meta-analysis of hypertension treatment trials. Arch Fam Med 1995;4:943–9.

4 Gueyffier F, Boutitie F, Boissel JP, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997;126:761–7.

5 Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997;277:739–45.

6 Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke 2003;34:2741–8.

7 Turnbull F, Neal B, Algert C, et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–35.

8 Cheung BM, Cheung GT, Lauder IJ, et al. Meta-analysis of large outcome trials of angiotensin receptor blockers in hypertension. J Hum Hypertens 2006;20:37–43.

9 Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534–44.

10 Sega R. Efficacy and safety of eprosartan in severe hypertension. Eprosartan Multinational Study Group. Blood Press 1999;8:114–21.

11 Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens 2003;21:1055–76.

12 Wang JG, Staessen JA. Benefits of antihypertensive pharmacologic therapy and blood pressure reduction in outcome trials. J Clin Hypertens 2003;5:66–75.

13 Lawes CM, Rodgers A, Bennett DA, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 2003;21:707–16.

14 Lawes CM, Bennett DA, Feigin VL, et al. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:776–85.

15 Chalmers J, MacMahon S, Bousser M-G, et al. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033–41.

16 Schrader J, Lüders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 2005;36:1218–26.

17 Schmeider RE. Mechanisms for the clinical benefits of angiotensin receptor II blockers. Am J Hypertens 2005;18:720–30.

18 Hunink MG, Bult JR, de Vries J, et al. Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. Med Decis Making 1998;18:337–46.

19 D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J 2000;139:272–81.

20 Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312–18.

21 Sacco RL, Wolf PA, Kannel WB, et al. Survival and recurrence following stroke. The Framingham study. Stroke 1982;13:290–5.

22 Cupples LA, D'Agostino RB, Kiely D, Survival following initial cardiovascular events—The Framingham Study Section 35. In: Kannel WB, Wolf PA, Garrison RJ, eds. The Framingham Study—An Epidemiological Investigation of Cardiovascular Disease. Bethesda, MD: US National Institutes of Health, 1988.

23 World Health Organization. Life tables for WHO member states. 2007. Available from: http://www.who.int/whosis/database/life_tables/life_tables.cfm [Accessed November 19, 2007].

24 Hardie K, Hankey GJ, Jamrozik K, et al. Ten-year survival after first-ever stroke in the Perth community stroke study. Stroke 2003;34:1842–6.

25 Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32:2735–40.

26 L'Ecuyer P, Zauberman G, Ariely D, et al. Good parameters and implementations for combined multiple recursive random number generators. Oper Res 1999;47:159–64.

27 Conlin PR, Gerth WC, Fox J, et al. Four-Year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other artihypertensive drug classes. Clin Ther 2001;23:1999–2010.

28 Sappok T, Faulstich A, Stuckert E, et al. Compliance with secondary prevention of ischemic stroke: a prospective evaluation. Stroke 2001;32:1884–9.

29 Annemans L, Crott R, Degraeve D, et al. Recommended structure for reporting economic evaluation on pharmaceuticals in Belgium. Pharm World Sci 2002;24:5–7.

30 Schulenburg J-M, Greiner W, Jost F, et al. German recommendations on health economic evaluation—third and updated version of the Hanover Consensus. Gesundheitsökon Qualitätsmanage 2007;12:285–90.

31 Department of pharmacoeconomics of the Norwegian Medicines Agency. Norwegian guidelines for pharmacoeconomic analysis in connection with applications for reimbursement. 2005. Available from: http://www.legemiddelverket.no/templates/InterPage____25644.aspx [Accessed December 10, 2007].

32 Rovira J, Antonanzas F. Economic analysis of health technologies and programmes. A Spanish proposal for methodological standardisation. Pharmacoeconomics 1995;8:245–52.

33 Swedish Pharmaceutical Benefits Board. General guidelines for economic evaluations—Sweden. 2003. Available from: http://

www.lfn.se/upload/English/ENG_lfnar2003-eng.pdf [Accessed November 20, 2007].
34 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal: section 5: Clinical and cost effectiveness and NHS impact. 2004. Available from: http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf [Accessed December 12, 2007].
35 Evans C, Tavakoli M, Crawford B. Use of quality adjusted life years and life years gained as benchmarks in economic evaluations: a critical appraisal. Health Care Manag Sci 2004;7:43–9.
36 Socialstyrelsen. The Swedish National Board of Health and Welfare's guidelines for cardiac care—support for decisions in setting priorities. 2004. Available from: http://www.sos.se/ [Accessed May 3, 2008].
37 Persson U, Hjelmgren J. Hälso- och sjukvården behöver kunskap om hur befolkningen värderar hälsan. Läkartidningen 2003;100:3436–7.
38 Lundin D. Kostnadseffektivitet som kriterium för subvention av läkemedel—en bra idé? ekonomiskdebatt 2004;34:32–40.
39 Bastian H, Bender R, Kaiser T, et al. IQWiG Methoden Version 1.0. Cologne, Germany: Institute for Quality and Efficiency in Health Care, 2005. Available from: http://www.iqwig.de/download/Methoden_IQWiG_V-1-0.pdf [Accessed December 13, 2007].
40 Bellach BM. [The 1998 Federal Health Survey. Experiences, results, perspectives]. Gesundheitswesen 1999;61:Spec No:S55–6.
41 Hallan H, Romundstad S, Kvenild K, et al. Microalbuminuria in diabetic and hypertensive patients and the general population—consequences of various diagnostic criteria—the Nord-Trondelag Health Study (HUNT). Scand J Urol Nephrol 2003;37:151–8.
42 Kvenild K, Romundstad S, Midthjell K, et al. Microalbuminuria in treated hypertensives: only a mirror image of cardiovascular risk? The HUNT Study, Norway. Scand J Prim Health Care 2006;24:145–53.
43 Kuch B, Schunkert H, Muscholl M, et al. [Distribution, determinants and reference values of left ventricular parameters in the general population—results of the MONICA/KORA echocardiography studies]. Gesundheitswesen 2005;67(Suppl. 1):S68–73.
44 Cederholm J, Nilsson PM, Anderberg CP, et al. Blood pressure and other cardiovascular risk factors among treated hypertensives in Swedish primary health care. Scand J Prim Health Care 2002;20:224–9.
45 Lindblad U, Rastam L, Ryden L, et al. Control of blood pressure and risk of first acute myocardial infarction: skaraborg hypertension project. BMJ 1994;308:681–6.
46 Nilsson P, Andersson DK, Andersson PE, et al. Cardiovascular risk factors in treated hypertensives—a nation-wide, cross-sectional study in Sweden. J Intern Med 1993;233:239–45.
47 Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949–53.
48 Ostgren CJ, Merlo J, Rastam L, et al. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes Obes Metab 2004;6:367–74.
49 Thomas F, Renaud F, Benefice E, et al. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 2001;73:271–90.
50 Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. Stroke 2004;35:1548–51.
51 Lidfeldt J, Nyberg P, Nerbrand C, et al. Socio-demographic and psychosocial factors are associated with features of the metabolic syndrome. The Women's Health in the Lund Area (WHILA) study. Diabetes Obes Metab 2003;5:106–12.
52 Lozano JV, Redon J, Cea-Calvo L, et al. [Risk assessment for a first stroke in Spanish hypertensive population in primary care. The ERIC-HTA study]. Med Clin (Barc) 2005;125:247–51.
53 Bog-Hansen E, Lindblad U, Bengtsson K, et al. Risk factor clustering in patients with hypertension and non-insulin-dependent diabetes mellitus. The Skaraborg Hypertension Project. J Intern Med 1998;243:223–32.
54 National Centre for Social Research, Department of Epidemiology and Public Health at the Royal Free and University College Medical School. Commissioned by Department of Health, England health survey 2003. UK data archive, 2004.
55 Ostgren CJ, Lindblad U, Melander A, et al. Survival in patients with type 2 diabetes in a Swedish community: skaraborg hypertension and diabetes project. Diabetes Care 2002;25:1297–302.
56 Ceinos AM, Acosta EE, Martin PC, et al. [Risk factors related to osteoporosis and age of onset of menopause in the general population]. Aten Primaria 1999;24:140–4.
57 Rodstrom K, Bengtsson C, Milsom I, et al. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. Menopause 2003;10:538–43.
58 Tuesca-Molina R, Guallar-Castillon P, Banegas-Banegas JR, et al. [Factors associated with the control of hypertension among older Spaniards, over 60 years of age]. Rev Esp Salud Publica 2006;80:233–42.
59 Thomas F, Renaud F, Benefice E, et al. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 2001;73:271–90.
60 Burström K, Johannesson M, Diderichsen F. Health-related quality of life by disease and socio-economic group in the general population in Sweden. Health Policy 2001;55:51–69.
61 Bell CM, Chapman RH, Stone PW, et al. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses. Med Decis Making 2001;21:288–94.
62 FPS Economy, SMEs, Self-employed and Energy. Healthcare cost index Belgium (Indice santé). 2007. Available from: http://economie.fgov.be/ [Accessed November 29, 2007].
63 Federal Statistical Office. Healthcare cost index Germany. 2007. Available from: http://www.destatis.de [Accessed November 29, 2007].
64 Statistics Norway. Healthcare cost index Norway. 2007. Available from: http://www.ssb.no [Accessed November 29, 2007].
65 The National Statistics Institute. Healthcare cost index Spain. 2007. Available from: http://www.ine.es [Accessed November 29, 2007].
66 Statistics Sweden. Healthcare cost index Sweden. 2007. Available from: http://www.scb.se/ [Accessed November 29, 2007].
67 The Office for National Statistics. Healthcare cost index UK. 2007. Available from: http://www.statistics.gov.uk [Accessed November 29, 2007].
68 Fjaertoft H, Indredavik B. [Cost-estimates for stroke]. Tidsskr Nor Laegeforen 2007;127:744–7.
69 The European Central Bank. Euro foreign exchange reference rates for Norway, Sweden and the UK. 2007. Available from: http://www.ecb.de/stats/exchange/eurofxref/html/index.en.html [Accessed November 29, 2007].
70 Institut national d'assurance maladie-invalidité (INAMI). Drug costs Belgium: Liste des spécialités pharmaceutiques remboursables. 2007. Available from: http://www.inami.fgov.be [Accessed November 29, 2007].
71 Rote Liste® Service GmbH Frankfurt/Main. Drug costs Germany: ROTE LISTE®—Arzneimittelsverzeichnis für Deutschland (online). 2007. Available from: http://www.rote-liste.de [Accessed November 29, 2007].
72 Norwegian Medicines Agency (NoMA). Drug costs Norway: Prisdatabase (PIA). 2007. Available from: http://www.legemiddelverket.no [Accessed November 29, 2007].
73 IMS Health. Drug costs Spain: Spanish IMS drug cost database. 2007. Available from: http://www.imshealth.com [Accessed November 20, 2007].
74 Pharmaceutical Benefits Board (LFN). Drug costs Sweden: Sök priser på läkemedel. 2007. Available from: http://www.lfn.se [Accessed November 29, 2007].
75 National Health Service England and Wales. Drug costs UK: the NHS Electronic Drug Tariff. 2007. Available from: http://www.ppa.org.uk [Accessed November 29, 2007].
76 Staessen JA, Den Hond E, Celis H, et al. Antihypertensive treatment based on blood pressure measurement at home or in the

physician's office: a randomized controlled trial. JAMA 2004; 291:955–64.
77 Association of Statutory Health Insurance Physicians. German physician fee schedule (EBM 2000 plus), version of the fourth quarter 2007. 2007. Available from: http://www.kbv.de [Accessed November 29, 2007].
78 Johannesson M, Meltzer D, O'Conor RM. Incorporating future costs in medical cost-effectiveness analysis: implications for the cost-effectiveness of the treatment of hypertension. Med Decis Making 1997;17:382–9.
79 Badia X, Bueno H, Gonzalez J Jr, et al. [Short-and long-term cost-effectiveness analysis of adding clopidogrel to standard therapy in acute coronary syndrome patients in Spain]. Rev Esp Cardiol 2005;58:1385–95.
80 UK Department of Health. NHS reference costs. 2006. Available from: http://www.dh.gov.uk [Accessed November 29, 2007].
81 Levy E, Gabriel S, Dinet J. The comparative medical costs of atherothrombotic disease in European countries. Pharmacoeconomics 2003;21:651–9.
82 Muls E, Van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. Atherosclerosis 1998;137(Suppl.):S111–16.
83 Schoenen J, Gianni F, Schretlen L, et al. Cost estimates of brain disorders in Belgium. Acta Neurol Belg 2006;106:208–14.
84 Kolominsky-Rabas PL, Heuschmann PU, Marschall D, et al. Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry: the Erlangen Stroke Project. Stroke 2006;37:1179–83.
85 Mullins CD, Sikirica M, Seneviratne V, et al. Comparisons of hypertension-related costs from multinational clinical studies. Pharmacoeconomics 2004;22:1001–14.
86 Ray JA, Valentine WJ, Secnik K, et al. Review of the cost of diabetes complications in Australia, Canada, France, Germany, Italy and Spain. Curr Med Res Opin 2005;21:1617–29.
87 Rossnagel K, Nolte CH, Muller-Nordhorn J, et al. Medical resource use and costs of health care after acute stroke in Germany. Eur J Neurol 2005;12:862–8.
88 Carod-Artal FJ, Egido-Navarro JA, Gonzalez-Gutierrez JL, et al. [Direct cost of cerebrovascular disease during the first year of follow-up]. Rev Neurol 1999;28:1123–30.
89 Andersson A, Levin LA, Oberg B, et al. Health care and social welfare costs in home-based and hospital-based rehabilitation after stroke. Scand J Caring Sci 2002;16:386–92.
90 Ghatnekar O, Persson U, Glader EL, et al. Cost of stroke in Sweden: an incidence estimate. Int J Technol Assess Health Care 2004;20:375–80.
91 Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): predicting long-term costs from functional status. Stroke 1999;30:2574–9.
92 Youman P, Wilson K, Harraf F, et al. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003;21(Suppl. 1):S43–50.
93 Zethraeus N, Molin T, Henriksson P, et al. Costs of coronary heart disease and stroke: the case of Sweden. J Intern Med 1999;246:151–9.
94 Finnern HW, Sykes DP. The hospital cost of vertebral fractures in the EU: estimates using national datasets (includes the cost per hospital day in Belgium). Osteoporos Int 2003;14:429–36.
95 Balestat G, Canaud MC, Lafortune G, et al. OECD Health Data 2006: Mean length of stay for TIA in Belgium. Paris: Organisation for Economic Co-operation, 2006.
96 Dodel RC, Haacke C, Zamzow K, et al. Resource utilization and costs of stroke unit care in Germany. Value Health 2004;7:144–52.
97 Institut für das Entgeltsystem im Krankenhaus (Institute for the Hospital Renumeration System). G-DRG case weights 2007. 2007. Available from: http://www.g-drg.de/ [Accessed November 29, 2007].
98 Norwegian Directorate for Health and Social Affairs (Sosial-og helsedirektoratet). Hospital funding 2007 (Innsatsstyrt finansiering 2007). 2007. Available from: http://www.shdir.no/ [Accessed August 27, 2007].
99 Navarro Espigares JL, González López JM, Hernandez Torres L, et al. Cost-Effectiveness Analysis of Ambulatory Treatment Based on Eco-Doppler Examination for Patients with Transient Ischemic Attack. The 115th annual meeting of the American Public Health Association, 2007.
100 Swedish National Board for Health and Welfare (Socialstyrelsen). Swedish NordDRG weights for 2007. 2007. Available from: http://www.socialstyrelsen.se [Accessed August 27, 2007].
101 Stockholm Country Council. Estimated DRG cases and estimated costs per DRG point of hospitals within the Stockholm region. 2007. Available from: http://www.sll.se/ [Accessed August 27, 2007].
102 Allender S, Scarborough P, Boxer A, et al., Economic Costs, Coronary Heart Disease Statistics. London: The British Heart Foundation, 2007.
103 Annemans L, Backer W, Rompay W, et al. Evaluation of the costs of coronary heart disease in Belgium. Value Health 1998;1:33.
104 Klever-Deichert G, Hinzpeter B, Hunsche E, et al. [Costs of coronary heart diseases over the remaining life time in coronary heart disease cases—an analysis of the current status of coronary heart disease cases in Germany from the social perspective]. Z Kardiol 1999;88:991–1000.
105 Taylor MJ, Scuffham PA, McCollam PL, et al. Acute coronary syndromes in Europe: 1-year costs and outcomes. Curr Med Res Opin 2007;23:495–503.
106 Clarke P, Gray A, Legood R, et al. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabet Med 2003;20:442–50.
107 Koster I, Hauner H, von Ferber L. [Heterogeneity of costs of diabetic patients: the Cost of Diabetes Mellitus Study]. Dtsch Med Wochenschr 2006;131:804–10.
108 Gomez-Gerique JA, Casciano R, Stern L, et al. A pharmacoeconomic evaluation of the effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes in Spain. Eur J Health Econ 2004;5:278–84.
109 Jönsson B. Measurement of health outcome and associated costs in cardiovascular disease. Eur Heart J 1996;17(Suppl. A):S2–7.
110 Levine B. Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension. Curr Med Res Opin 2001;17:8–17.
111 Neutel JM. Prescribing patterns in hypertension: the emerging role of fixed-dose combinations for attaining BP goals in hypertensive patients. Curr Med Res Opin 2008;24:2389–401.
112 Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther 2007;29:563–80.
113 Mann JFE, Schmeider RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. Lancet 2008;372:547–3.
114 National Collaborating Centre for Chronic Conditions. Hypertension: Management in Adults in Primary Care: Pharmacological Update. London: Royal College of Physicians, 2006.