Economic evaluation of ASCOT-BPLA: antihypertensive treatment with an amlodipine-based regimen is cost effective compared with an atenolol-based regimen

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ABSTRACT

Objective: To compare the cost effectiveness of an amlodipine-based strategy and an atenolol-based strategy in the treatment of hypertension in the UK and Sweden.

Design: A prospective, randomised trial complemented with a Markov model to assess long-term costs and health effects.

Setting: Primary care.

Patients: Patients with moderate hypertension and three or more additional risk factors.

Interventions: Amlodipine 5–10 mg with perindopril 4–8 mg added as needed or atenolol 50–100 mg with bendroflumethiazide 1.25–2.5 mg and potassium added as needed

Main outcome measures: Cost per cardiovascular event and procedure avoided, and cost per quality-adjusted life-year gained.

Results: In the UK, the cost to avoid one cardiovascular event or procedure would be €18 965, and the cost to gain one quality-adjusted life-year would be €21 875. The corresponding figures for Sweden were €13 210 and €16 856.

Conclusions: Compared with the thresholds applied by NICE and in the Swedish National Board of Health and Welfare's Guidelines for Cardiac Care, an amlodipine-based regimen is cost effective for the treatment of hypertension compared with an atenolol-based regimen in the population studied.

Optimal first-line treatment and subsequent sequencing of antihypertensive drugs has been controversial for decades. This is reflected in different recommendations made in recent guidelines world wide.[1–4] Before 1995, almost all randomised trial evidence on hypertension management related to diuretic agents and to a lesser extent β-blockers.[5] However, newer drug classes were increasingly being used and have consequently been evaluated in major trials. Enthusiasm for any potential advantages of the newer agents (at least on surrogate end points) has been tempered in some situations by concerns over their increased cost. Despite the reality that the majority of hypertensive patients need at least two agents to reach currently recommended targets, until recently no trial data were available to compare the benefits of newer combinations of drugs with the standard most commonly used regimen of a β-blocker with a diuretic.

The Blood-Pressure-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) randomised 19 257 patients to receive either amlodipine 5–10 mg adding perindopril 4–8 mg as needed to reach blood pressure targets, or atenolol 50–100 mg adding bendroflumethiazide 1.25–2.5 mg and potassium as needed.

Patients included in the trial were men and women aged between 40 and 79 years, with either untreated hypertension (a systolic blood pressure ⩾160 mm Hg or a diastolic blood pressure ⩾100 mm Hg) or treated hypertension with a systolic blood pressure ⩾140 mm Hg or a diastolic blood pressure ⩾90 mm Hg. Patients were also required to have at least three of the following risk factors: male sex, age above 55 years, smoking, left ventricular hypertrophy, other abnormalities on electrocardiogram, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, microalbuminuria or proteinuria, a ratio of plasma total cholesterol to high-density lipoprotein-cholesterol of 6 or higher, or a family history of early coronary heart disease. The trial was stopped prematurely after a median of 5.5 years owing to a significant beneficial effect of the amlodipine-based regimen on all-cause mortality (hazard ratio (HR) = 0.89, 95% CI 0.81 to 0.99). The HR for the primary end point (myocardial infarction (MI) including silent events and fatal coronary heart disease) was 0.90 (95% CI 0.79 to 1.02) in favour of the amlodipine-based regimen. There were also significant reductions in the number of fatal and non-fatal strokes (HR = 0.77, 95% CI 0.66 to 0.89), total cardiovascular events and procedures (HR = 0.84, 95% CI 0.78 to 0.90) and in the incidence of new-onset diabetes in the amlodipine-based group (HR = 0.70, 95% CI 0.63 to 0.78).[6]

Looking only at the cost of medication, newer treatments (such as amlodipine and perindopril) are typically more expensive than their older comparators (such as atenolol and thiazides) but in ASCOT they induced better preventive effects on all major cardiovascular outcomes. To make a rational decision when allocating resources in healthcare, it is necessary to take potential savings due to decreased morbidity and mortality into consideration. If the net costs still indicate that the newer strategy adds costs, a formal estimation of the cost effectiveness of the treatment is necessary. The scope of this study was to conduct an

Table 1 Drug costs (€) used in the analysis

	UK	Sweden
Amlodipine 5 mg	0.69	0.54
Amlodipine 10 mg	1.03	0.83
Perindopril 4 mg	0.54	0.81
Perindopril 8 mg	1.09	0.81
Doxazosin GITS 4 mg	0.49	0.54
Doxazosin GITS 8 mg	0.49	1.07
Atenolol 50 mg	0.05	0.04
Atenolol 100 mg	0.04	0.07
BFZ/K+ 1.25 mg	0.05	0.13
BFZ/K+ 2.50 mg	0.11	0.26

Source: Swedish Drug Tariff (FASS) and Monthly Index of Medical Specialities.[7 8]
BFZ/K, bendroflumethiazide/potassium.

economic evaluation of ASCOT-BPLA. This prospective economic evaluation was a prespecified analysis of the trial. Analyses were conducted for the UK and Sweden, the two largest contributors of patients to the trial.

MATERIAL AND METHODS

Two approaches were taken in the analysis of the cost effectiveness of the amlodipine-based regimen: A within-trial analysis estimating the costs and events avoided during the trial period; and a modelling approach extrapolating costs and the potential benefits of avoiding events on long-term survival and quality-adjusted survival over the lifetime of the patients.

In the within-trial analysis, resources used during the trial period (and being recorded on the case report forms) were multiplied by their unit cost, and an average cost per patient was estimated. Resources used included use of study drug, endpoint-related hospitalisations, non-endpoint-related hospitalisations and concomitant drugs using standard published sources for unit costs.[7–11] Prices are expressed in euros (€), using the average exchange rates during 2006 to convert British pounds and Swedish kronor to the € (€1 = £0.68, Kr9.25).[12] For a more in-depth description of the costing approach, please refer to our previously reported study of the lipid-lowering arm of ASCOT.[13] In the within-trial analysis, we used the average total number of events per patient during the trial as the measure of effectiveness.

To estimate long-term cost and effects, a Markov model[14] consisting of six states was constructed: event-free, diabetes, MI, coronary revascularisation, stroke and death. The four event states (MI, diabetes, revascularisation and stroke) are implemented as tunnel states to allow for differentiation of costs and lost utility over time. Patients in the event-free state stand a risk of having any of the four events, which in the case of strokes and MIs may or may not be fatal. Patients in the event states either die or remain within their current state for the rest of the simulation. This means that only first events are explicitly incorporated in the model. Patients developing diabetes (or having diabetes at baseline), have a subsequent risk of developing MI, stroke or undergoing revascularisation.

The transition probabilities used in the model are derived from the clinical trial through survival modelling, with the exception of the risk of an event being fatal which was estimated through logistic regression. These data are available online. Mortality following an event was estimated based on the entire trial sample (ie, not estimated separately by treatment arm). This means that we are assuming no difference in mortality after an event for the two treatments. Any potential survival benefit is thus only caused by a difference in the risk of events. To avoid an underestimation of the mortality in higher age groups which were not represented in the trial, the model is programmed so that mortality does not fall below that of the general population (stratified by age and gender).[15]

The cost of the study drug is based on the mean number of days for which each dose was prescribed during the trial period and the daily cost of the drug (table 1). Because perindopril is not available on the Swedish market it was assumed to have the same relative price compared with the other study drugs as in the UK (€0.81 per 4 mg). We also conducted analyses where it was assumed to have the same price as the two most commonly used ACE inhibitors in Sweden (ramipril 10 mg and enalapril 20 mg, €0.18 and €0.05, respectively).

Costs for events were estimated by comparing the resource consumption during the year before the event to that 1 and

Table 2 Mean costs, number of events and incremental cost effectiveness during the trial period

	UK		Sweden	
	Amlodipine-based	Atenolol-based	Amlodipine-based	Atenolol-based
Mean cost (€) per patient				
Study drug	2440 (2418 to 2462)	599 (590 to 608)	2850 (2820 to 2881)	1274 (1254 to 1294)
Outpatient visits	2440 (2425 to 2455)	2525 (2509 to 2543)	2240 (2227 to 2254)	2318 (2303 to 2334)
Concomitant drugs	2167 (2127 to 2207)	2418 (2375 to 2459)	2396 (2353 to 2438)	2649 (2604 to 2693)
DRG hospitalisations	766 (718 to 816)	1036 (976 to 1097)	1068 (1000 to 1136)	1448 (1364 to 1531)
Other hospitalisations	3352 (3148 to 3557)	3447 (3221 to 3673)	2523 (2369 to 2678)	2595 (2425 to 2765)
Total cost	11 166 (10 942 to 11 391)	10 026 (9775 to 10 277)	11 078 (10 889 to 11 267)	10 283 (10 071 to 10 496)
Events per patient				
Primary end point*	0.047 (0.043 to 0.052)	0.054 (0.049 to 0.059)	0.047 (0.043 to 0.052)	0.054 (0.049 to 0.059)
All events and procedures	0.216 (0.203 to 0.229)	0.276 (0.261 to 0.291)	0.216 (0.203 to 0.229)	0.276 (0.261 to 0.291)
Cost effectiveness†				
Cost to avoid one primary event	161 364 (74 752 to 4 327 288)		112 402 (49 597 to 3 106 460)	
Cost to avoid one event or procedure	18 965 (11 591 to 31 855)		13 210 (7262 to 23 392)	

Results are shown as mean values (95% confidence intervals).
*Silent and non-silent myocardial infarction and fatal coronary heart disease.
†Compared with atenolol-based treatment.
DRG, diagnosis-related group (potentially endpoint-related hospitalisations).

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Table 3 Predicted per patient life-time costs (€), health outcomes and incremental cost effectiveness

	UK*		Sweden†	
	Amlodipine-based	**Atenolol-based**	**Amlodipine-based**	**Atenolol-based**
Costs				
Drug cost	3107	1069	4470	2480
Event cost	2268	2471	3117	3361
Indirect costs	NA	NA	215	278
Total cost	5376	3540	7802	6119
Health outcomes				
Life expectancy	11.69	11.59	12.49	12.37
Quality-adjusted life expectancy	8.84	8.76	9.82	9.72
Incremental cost effectiveness‡				
Cost per LYG (€)	17 857		14 022	
Cost per QALY gained (€)	21 875		16 856	

*Costs and effects discounted at 3.5% a year.
†Costs and effects discounted at 3% a year.
‡Relative to atenolol-based regimen.
LYG, life-years gained; NA, not applicable; QALY, quality-adjusted life-year.

2 years after it (data available online). Health economic guidelines in Sweden and the UK differ in their view of costs caused by lost production (indirect costs),[16 17] which Swedish guidelines recommend including, whereas the UK guidelines do not. Therefore only Swedish analyses incorporate indirect costs. This was based on a study of indirect costs and quality of life in Swedish ASCOT patients.[18] Two measures of health outcomes were included in the model: life-years gained based on the predicted survival in the two treatment groups and quality-adjusted life-years (QALYs) gained. In the latter case each life-year is weighted according to the health status of the patients. The weights used (called utility weights) are normally between 1 and 0, where 1 represents a health state equal to perfect health and 0 represents death. Event-free patients are assumed to have the same utility weights as people in the general population (adjusted for age and gender).[19 20] To account for the effect of events, data from the above mentioned survey of Swedish patients were used.[18] This study indicated that patients with MI had moved back to their original utility level after 1 year, while no such improvement was seen in patients with stroke. No data were collected for patients undergoing coronary revascularisation. We therefore assume that they had a slightly smaller decrease in utility than the average patients with MI, based on results from another Swedish survey.[21]

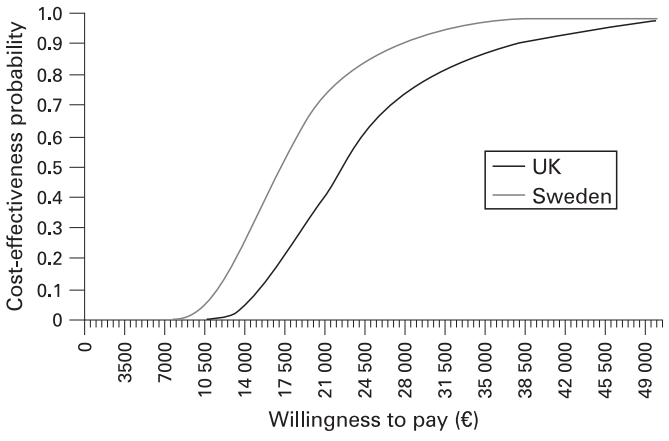

Figure 1 Cost-effectiveness acceptability curve indicating the probability that the amlodipine-based strategy is cost effective compared with the atenolol-based strategy at different willingness-to-pay thresholds to gain one quality adjusted life-year.

Uncertainty was incorporated into the model through probabilistic analysis using second-order Monte Carlo simulation. One thousand simulations were performed. In each of the simulations, each variable was sampled from its underlying distribution. The distributions were estimated by performing non-parametric bootstrapping of each variable.[22] Uncertainty was reported in the form of cost-effectiveness acceptability curves.[23]

In the base case, a cohort similar to that of the clinical trial was analysed (63 years of age, 19% female, 27% diabetic). Patients were assumed to be treated for 6 years, and followed up for the remainder of their life. In the long-term model, costs and effects were discounted at 3.5% a year in the UK and 3% a year in Sweden in accordance with guidelines in the two countries.

RESULTS

Table 2 shows the results of the within-trial analysis. As expected in the amlodipine-based group, the cost of the study drugs was higher than with the atenolol-based strategy, but there were lower costs for all other resource categories, thus offsetting 38–50% of the drug costs during the 5.5-year trial period.

Table 3 shows modelled lifelong predictions of costs, outcomes and cost effectiveness. The chief explanatory factor for the difference in survival and quality-adjusted survival is the difference in discounting recommended in the UK and Swedish guidelines (3.5% and 3% a year). This also affects the total predicted costs. The inclusion of indirect costs in the Swedish analysis is of minor importance owing to the mean age of the population (63 years) when included in the trial.

The cost-effectiveness acceptability curve in fig 1 shows the probability, given our data that the amlodipine-based strategy is cost effective for different levels of willingness-to-pay to gain one QALY. The difference between the UK and Sweden is once again mainly owing to the difference in discount rates, where the higher rate used in the UK leads to a lower valuation of future cost offsets and health gains compared with Sweden, and

thus a lower probability of the strategy being considered cost effective.

The assumptions in the model were tested in one-way sensitivity analyses. These indicated that the most sensitive variable is the proportion of women in the population, followed by the discounting factor used (data available online). In an all-female population, the incremental cost-effectiveness ratio (ICER) was €32 000 per QALY in the UK and €24 178 per QALY in Sweden. Factors such as the average age, changes in the costs caused by events and the utility reduction caused had limited impact on the results, as had extrapolating the duration of the intervention beyond the trial period. When the price of enalapril or ramipril was used as proxy for the price of perindopril in Sweden this led to lower cost-effectiveness ratios (€5964 and €3606 per QALY gained), owing to the low prices of these drugs (generic enalapril is the cheapest antihypertensive drug on the Swedish market). The introduction of generic amlodipine also has a large impact on the results. At a price of €0.10 per day in Sweden and €0.15 per day in the UK the cost to gain one QALY becomes €7257 and €8372 in the respective countries.

DISCUSSION

In the UK, our study indicates a cost of €18 965 to prevent one cardiovascular event or procedure, or €21 875 to gain one QALY during 6 years of treatment with the amlodipine-based compared with the atenolol-based regimen. This falls well below the threshold value of £20 000 (€29 000) per QALY included in the most recent NICE guidelines to indicate cost effectiveness.[17] The corresponding figures were €13 210 and €16 856 in Sweden, where the National Board of Health and Welfare has published guidance for prioritisations in cardiovascular medicine.[24] In this guidance an ICER below Kr100 000/QALY (€11 000) was classified as low, and a ratio below Kr500 000/QALY (€55 000) as moderate. Using these criteria, the cost-effectiveness ratio in our Swedish analyses fall just above the ''low'' threshold.

There is reason to believe that the cost-effectiveness ratios reported here are somewhat overestimated. Although the model incorporates new-onset diabetes as an end point, the costs associated with the microvascular complications due to diabetes are not included since they are likely to occur after the end of the trial. Diabetes is also associated with excess non-cardiovascular mortality, which is not incorporated here. Indeed, excluding the additional cost for diabetes has a limited impact on the results of our model, leading to an increase in the ICER of about €100. Using the cost reported in patients with no or microvascular complications only (assuming macrovascular complications are captured in the events costs of our model), which was reported in the CODE-2 in Sweden (€1762), gives an ICER of €16 450. This may still be an underestimation, as the largest cost increase in CODE-2 was observed for patients with both micro- and macrovascular complications.[25] Costs included were based on the data collected in the trial which has the advantage of giving very high internal validity. Some potentially important costs were not collected, and are thus omitted from the event costs. This includes costs for rehabilitation following a stroke and costs for admittance to nursing home facilities. Furthermore, with the expiration of the patent on amlodipine, drug prices have fallen. This will of course lead to even more beneficial cost-effectiveness ratios. For example, in our model, a reduction in the price of amlodipine by 30% would give a cost-effectiveness ratio of €17 000/QALY in the UK and €13 500/QALY in Sweden. Indeed, with the current price of €0.10 per day for amlodipine in Sweden and €0.15 in the UK the cost effectiveness ratio would be €7257/QALY in Sweden and €8372/QALY in the UK.

Some authors have argued for the inclusion of costs associated with increased survival (consumption minus production) to analyse properly the cost effectiveness from a societal perspective.[26 27] Such data are available for Sweden.[28] Including them in the analysis increases the cost-effectiveness ratio somewhat: €15 900 per QALY gained.

CONCLUSION

Based on the threshold values for cost effectiveness employed by the authorities in Sweden and the UK, an amlodipine-based treatment regimen appears to be cost effective compared with an atenolol-based regimen in patients with moderate hypertension and additional risk factors.

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Competing interests: PL, MB, TK, NRP, BD, PSS, HW and BJ have served as consultants to, and received travel expenses, payment for speaking at meetings or funding for research from. pharmaceutical companies marketing antihypertensive drugs, including AstraZeneca, Sanofi-Aventis, Bayer, Bristol-Myers Squibb Co, Merck, Sharpe and Dohme, Novartis, Pfizer, Schering, and Servier. PL, MB, TK, NRP, BD, PSS, HW and BJ received financial support from Pfizer to cover administrative and staffing costs of ASCOT, and travel, accommodation expenses or both incurred by attending relevant meetings.

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