The cost-effectiveness of amlodipine treatment in patients with coronary artery disease

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Abstract

The objective of this paper was to quantify the impact on overall cardiovascular disease treatment costs resulting from the use of amlodipine in the coronary artery disease (CAD) population in the UK. A Markov cohort simulation model was developed to estimate the overall average healthcare costs of patients with CAD in the UK and to determine the cost-effectiveness of the use of amlodipine as part of their treatment regimen. Outcome probabilities used in the model were based on patient-level data from the Prospective Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). Cost estimates for in-patient and out-patient care associated with each outcome were applied to quantify the overall average healthcare cost for each arm of the study.

The hospitalisation rate per patient in the placebo cohort was 61.8% while that in the amlodipine cohort was 44.3%. This corresponds to an average cost per patient for cardiovascular disease (CVD) treatment of £1,858.64 for amlodipine patients and £1,800.49 for placebo patients over three years of follow-up. Calculations yield a cost per hospitalisation avoided of £331.67.

In conclusion, the inclusion of amlodipine in the treatment regimen for patients with CAD is expected to result in improved clinical outcomes through a marginal investment in cost.

Key words: coronary artery disease, amlodipine, healthcare costs, hospitalisation rates.

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Introduction

The United Kingdom (UK) has one of the highest death rates from heart disease in the world and the prevention of coronary heart disease has been a primary goal of the National Health Service (NHS).[1] Heart disease is the primary cause of death in the UK, with a British adult dying of heart disease every three minutes.[2] Diseases of the circulatory system account for more than 10% of NHS expenditure.[1]

As the rates of CAD have increased throughout the industrialised countries, the use of interventional treatments has expanded rapidly. In 1993 coronary artery bypass graft (CABG) surgery accounted for 62% of all surgical procedures performed in the UK. The number of CABG procedures increased by 14% between 1992 and 1993 to reach 299 procedures per million population.[3] In 1985 there were only 29 procedures per million population;[4] by 1995 it had reached 251 procedures per million population.[5] Most of the direct costs associated with treating cardiovascular disease are spent on in-patient care.

Due to the source of funding for healthcare in the UK, strong pressures exist for efficient allocation of the available resources. With this healthcare policy, choices have to be made about allocation of limited funds, especially as new, often more expensive, medical technologies are being developed. The best methods of prevention from both a health outcomes and economic perspective must be identified.

It may be possible to minimise the need for expensive revascularisation procedures by improving treatment protocols. Although the success rate of revascularisation is relatively high initially, these procedures can lead to adverse clinical outcomes and the need for further interventions. In a 1994 study by Hamm *et al,* it was found that further interventions were necessary within one year of follow-up in 44% of percutaneous transluminal coronary angioplasty (PTCA) patients and in 23% of CABG patients.[6] Though advances in techniques, such as the employment of stents, have improved prognosis, there remains a need for improved under-

standing of more cost-effective medical treatments, which can improve outcomes of revascularisation procedures.

The Prospective Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was a multicentre, randomised, placebo-controlled, double-masked clinical trial designed to test whether amlodipine would slow the progression of coronary artery disease.[7] Several end points were tracked for the study. The primary end point of the study was the change in the average minimal lumen diameter of target atherosclerotic lesions. Secondary outcomes included the change in average minimal diameter in all atherosclerotic segments, the rate of progression of atherosclerosis in the carotid arteries and the number of CVD-related events and procedures requiring hospitalisation. The trial was conducted in 825 patients in centres throughout the United States and Canada: 417 patients were assigned to the amlodipine group and 408 patients to the placebo group.

After three years of follow-up, PREVENT results showed that amlodipine treatment did have an effect on the secondary end points measured. Specifically, it was shown that amlodipine use significantly slowed the progression of carotid wall thickening and resulted in a reduction in the frequency of hospitalisation for confirmed unstable angina and coronary revascularisation. However, amlodipine was not shown to reduce angiographic progression of early coronary lesions significantly in patients with CAD, nor was there a significant reduction in the risk of death or major vascular events over the three-year course of the trial.[7]

Despite its failure to meet its primary objectives, the findings of PREVENT relating to the secondary clinical end points carry important implications with respect to the assessment of the health economic profile of amlodipine when used in a population with CAD. We therefore developed a Markov simulation model to utilise these data in an investigation of the cost implications associated with the use of amlodipine, and to weigh these costs against the demonstrated benefits through incremental cost-effectiveness analysis.

Methods

A Markov cohort simulation model was constructed using patient-level data from PREVENT to estimate the expected health outcomes of CAD cohorts on amlodipine or placebo over the course of the three-year trial time-period. The constantly changing health status of the subjects observed during PREVENT was analysed using Markov modelling techniques, which are able to incorporate time dependency into the probability and costs associated with each clinical outcome.

Clinical outcomes included in the analysis were: hospitalisation for angina, myocardial infarction (MI) and chronic heart failure (CHF), PTCA procedures, CABG surgery, non-CVD hospitalisations and death. The rate of occurrence of these outcomes was obtained from PREVENT. Occurrence of each outcome was analysed as a separate health state in the Markov model. Since Markov models require mutually exclusive health states in order to maintain model integrity, and because events and procedures are not mutually exclusive, health states were added to the model, which thus accounted for combinations of event- and procedure-related outcomes. In addition, health states to account for long-term follow-up care were included in the model for patients who would experience an event and/or a procedure and would not go on to experience another event and/or procedure in the next cycle of the model. Once completed, the clinical outputs of the model were validated against the clinical findings of PREVENT.

Since the PREVENT study did not provide economic data, it was necessary to develop cost estimates for each of the health states in the model in order to use the model and its clinical predictions for an assessment of the economic outcomes. Cost estimates for each health state were comprised of the cost of the acute in-patient care and out-patient follow-up care, including physician services, laboratory tests and drug treatment. Non-CVD hospitalisations were included in the analysis of outcomes but excluded from the economic analysis. Costs of the acute in-patient care associated with cardiovascular-related events and procedures were obtained from the 1999 National Schedule of Reference Costs of the NHS.[8] Healthcare resource consumption in the out-patient setting was based on surveys conducted with a panel of UK practitioners. The out-patient costs were evaluated for a six-month period using a modified Delphi panel approach. Five cardiologists, practising in different hospitals in the UK, were surveyed to estimate the type and frequency of healthcare resources consumed during the follow-up period for all possible patient outcomes. Physician estimates were pooled, and mean values were used to approximate the quantity of resources consumed in the follow-up period for each cardiovascular hospitalisation.

Next, costs were assigned to each resource to estimate the total cost of follow-up care for the outcomes being evaluated. The costs of these resources were assessed through consultation with three local health economists. Costs of drug treatment were ultimately obtained from the British National Formulary 37 (1999),[9] and the costs of laboratory tests and physician visits were based on data maintained at three hospitals in the UK.[10]

The results of the cost estimation step for each outcome are presented in table 1 (medical care) and table 2 (drug costs). For the drug cost analysis, patients allocated to amlodipine treatment were conservatively assumed to be taking a 10 mg daily dose of amlodipine every day throughout the simulation or until death. Other cardiovascular drug usage was assessed based on the actual usage observed during PREVENT. However, to adjust this analysis to be UK-specific, the physician panel was consulted to determine the commonly prescribed products in each drug class in the UK. Study drug usage and additional procedures, such as catheterisations, valve replacements and pacemaker placement, were not considered to be associated exclusively with any of the health states. Instead, they were added to the total cost of either the placebo or amlodipine cohorts based on the usage and/or number of occurrences during the PREVENT trial.

The model provides an estimation of the frequency, overall time and cost attributable to each health state. In this way, overall outcomes and costs are assessed and can be compared for each of the study arms over the duration of the clinical trial. A

Table 1. Direct medical costs for health states

Health state	Cost of state for six months
Angina	£1,869.97
Angina (long-term)	£326.83
Angina with CABG	£7,160.04
Angina with PTCA/stents/atherectomy	£4,958.34
MI	£3,486.88
MI (long-term)	£286.96
MI with CABG	£7,160.04
MI with PTCA/stents/atherectomy	£4,958.34
CHF	£3,626.86
CHF (long-term)	£755.83
CABG	£7,160.04
CABG (long-term)	£251.00
PTCA/stents/atherectomy	£4,958.34
PTCA (long-term)	£224.87

Table 2. Annual drug treatment costs

Cost of amlodipine	£230.68
Cost of 'other' cardiovascular drugs among amlodipine patients	£498.58
Cost of 'other' cardiovascular drugs among placebo patients	£554.35

1.5% discount rate was applied to the health outcomes to account for the time-value of life years and a 6% discount rate was used to account for the time-value of money.[1] Sensitivity and scenario analyses were conducted to test the impact of key assumptions and data inputs on the results. An additional analysis was also performed which examined costs and outcomes of patients over the course of a 'lifetime', by extrapolating clinical trial results for up to 30 years.

Assumptions

Before input into the model, the clinical data from PREVENT were adjusted to consider the impact of practice patterns in the UK. The rate of procedures undertaken in the PREVENT trial population is specific to the Canadian and US centres in which the study was conducted, and is likely to be different in other healthcare settings. In order to apply the findings of the trial to the UK population, corresponding UK-specific procedure rates were necessary. Since the PREVENT analysis tells us information about the rate of procedures in a specific CAD population, it would be necessary to have this same measure for a UK population of CAD patients in order to approximate the results in the UK healthcare setting.

This specific information was not readily available, so it was necessary to approximate its value using two other available measures. We sought to determine the rate of procedures in a given population with CAD in the UK but only the rate of procedures for the overall population was available. Dividing the rate of procedures for the total population by the rate of CAD in the total population yields an estimate of the rate of procedures in the CAD population. This figure was then used to adjust the rate of procedures in the PREVENT population to be more representative of the UK healthcare setting. We assumed that the rate of clinical events such as MI and stroke is largely dictated by the underlying pathophysiology of the disorder, and would therefore be minimally impacted by differences in practice patterns.

Table 3. Relative risks of CAD and procedure usage in the US and the UK

	Rate in US (per 100,000)	Rate in UK (per 100,000)	Relative risk (UK vs. US)	Adjusted* relative risk
CAD	282.5	477.4	1.69	
PTCA	176	50	0.28	0.17
CABG	218	63	0.29	0.17
Catheterisation	453	172	0.38	0.22
Pacemaker insertion	54.1	23.2	0.43	0.25
Valve replacement	29.1	7.6	0.26	0.15

* relative risks adjusted for CAD prevalence

Estimates of the applicable rates were obtained from the European Society of Cardiology's European registries of cardiovascular diseases and patient management (1999), and were validated through consultation with the physician panel.[5] Adjusting the results from the clinical trial according to the differences in the prevalence of CAD and differences in the usage of procedures between the US and the UK resulted in a decreased number of events. This was primarily because diagnostic and therapeutic procedures are used less often in the UK (table 3). In the UK, the likelihood that an individual will be treated with PTCA is 0.28 and with CABG is 0.29 times that of the US at the population level. Simultaneously, the prevalence of CAD at the population level is 1.69 times higher in the UK than in the US.[5]

Results

Patients in the amlodipine cohort had significantly fewer hospitalisations for CV-related events and procedures than their placebo counterparts ($p<0.001$). The placebo cohort experienced a total of 252 hospitalisations for unstable angina, CABG, PTCA, CHF and MI while their amlodipine counterparts experienced 184 hospitalisations (figure 1). In the placebo cohort the rate of hospitalisation was 0.618 hospitalisations per patient over the trial duration while that in the amlodipine cohort was 0.443 hospitalisations per patient. Hence, there were 28% fewer hospitalisations for the amlodipine cohort than for the placebo cohort. Non-CVD-related hospitalisations were higher in the amlodipine group, at 193 compared with 165 for placebo. However, the overall number of hospitalisations remained lower for amlodip-

Figure 1. Number of hospitalisations per outcome

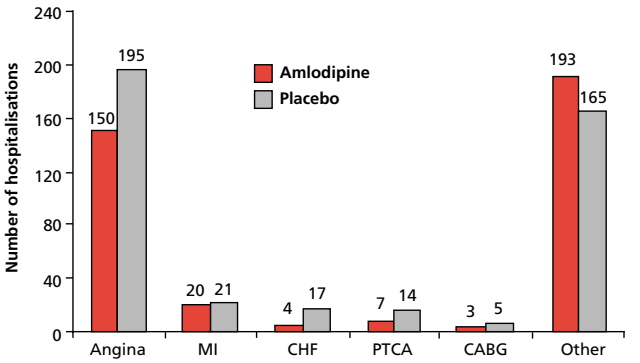


Figure 2. Cumulative CVD hospitalisations over three years

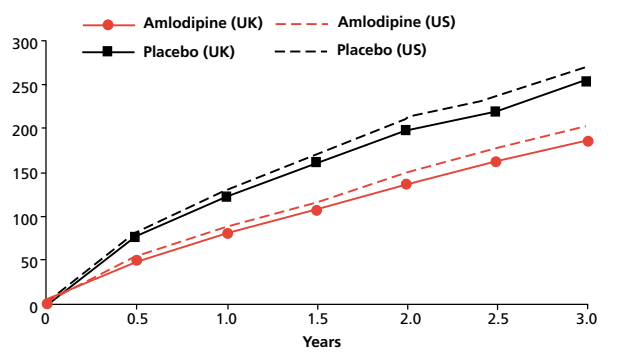


Figure 3. Expected three-year cost per patient

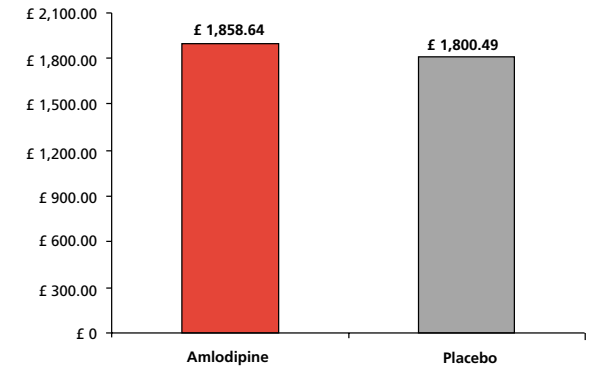
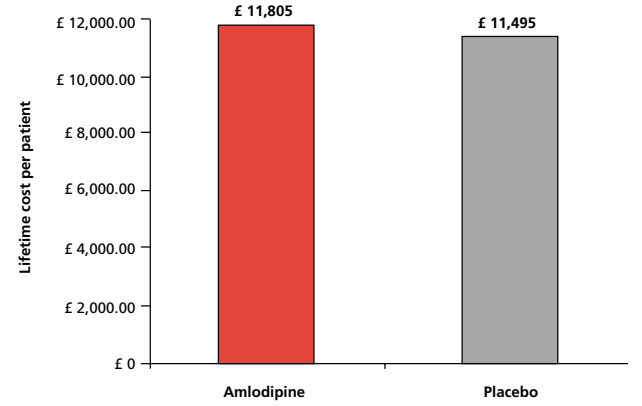


Figure 4. Cost of treatment per patient over 30 years



ine, at 378 hospitalisations in 417 patients versus 417 hospitalisations in 408 patients for placebo. Figure 2 demonstrates the difference in the number of CVD-related events and procedures, starting at six months and diverging over time. Of these hospitalisations, 79.1% were for unstable angina.

The use of amlodipine resulted in a significant reduction in CVD hospitalisations ($p<0.001$) at a marginal increase in cost. The net present value of the expected cost per patient over the three-year trial time period was £58.15 more for amlodipine patients than for placebo patients (figure 3). The total expected three-year cost per patient on amlodipine was £1,858.64 and the cost per patient on placebo was £1,800.49. Dividing the incremental cost for amlodipine patients into the incremental rate of CVD hospitalisations experienced by the placebo cohort [(£1,859 - £1,800)/(0.62 - 0.44)] amounts to a cost per hospitalisation avoided of £331.67. When the results were extrapolated out to 30 years for the lifetime model, the marginal differences in costs between the two cohorts did not differ greatly from the marginal differences in cost detected in the within-trial model. The net present value of the 30-year cost per patient was £11,805 for amlodipine patients and £11,495 for placebo patients (figure 4).

Sensitivity analyses

Univariate analyses revealed that results were robust to the UK-specific relative risks of interventional procedures (table 4). Changing the relative risks by +/-15% did not affect the rank order of the results. Results were insensitive to the costs of health states for MI, CHF, PTCA and CABG. Changes of +/-15% in the cost of events and hospitalisations did not alter the rank order of the results. Varying the discount rate for cost between 0% and 8% did not increase or decrease the total expected costs by more than 10% and rank order of results was not modified. Varying the discount rate for outcomes between 0% and 3% did not increase or decrease the total expected costs by more than 3% and the rank order of results was not modified.

Multivariate analysis revealed that the model was robust when multiple parameters were varied simultaneously (table 4). Transitional probabilities and relative risks were varied randomly

Table 4. Sensitivity analysis results

Variable	Cost for amlodipine patients	Cost for placebo patients
Univariate analysis		
Reference case	£1,859	£1,800
Relative risk varied by +/-15%	£1,851-1,867	£1,786-1,815
Direct costs varied by +/-15%		
- Angina	£1,766-1,951	£1,677-1,924
- MI	£1,836-1,881	£1,775-1,825
- PTCA	£1,847-1,871	£1,777-1,824
- CABG	£1,852-1,865	£1,788-1,813
Discount rate for costs varied between 0-8%	£1,807-2,032	£1,756-1,951
Discount rate for outcomes varied between 0-3%	£1,818-1,901	£1,765-1,837
CV medicines usage excluded from analyses	£1,859	£1,633
Timeline extended to 30 years	£11 805	£11 495
Multivariate analysis	£1,859 (£1,607–2,110)	£1,802 (£1,509–2,088)

Transitional probabilities varied within one standard deviation based on a normal distribution
Relative risks varied within one standard deviation based on a normal distribution
Direct health state costs varied +/-10% based on a uniform distribution

within one standard deviation based on a normal distribution. Costs of health states were varied randomly within +/-10% of the estimated cost based on a uniform distribution. For the cost per patient in the amlodipine group, 10 000 trial simulations yielded a mean value of £1,859 with a standard deviation of £128 and a range of £1,414 to £2,388. For these simulations, 95% of the values were between £1,607 and £2,110. For the cost per patient in the placebo group, 10 000 trial simulations yielded a mean value of £1,802 with a standard deviation of £147 and a range of £1,214 to £2,291. Some 95% of the values were between £1,509 and £2,088.

Extending the analysis out to 30 years increased overall costs accordingly but did not greatly alter the relative proportion of the difference in total cost between the two cohorts. In the three-year model, the difference in costs represented 3.1% of the total cost per patient in the amlodipine cohort; in the 30-year simulation, the difference represented 2.6% of the total cost (table 3).

A second scenario analysis examined the cost impact associated with the use of other non-study CVD medications. The net cost incurred by the use of 'other' cardiovascular drugs in each of the study arms was considered. Scenario analysis tested the robustness of the model by excluding the cost of concomitant medication in the analysis. This further increased the cost difference in favour of the placebo patients since the usage of 'other' medications was higher in the placebo arm (table 4). This analysis is inherently biased against the amlodipine arm since the event rates observed in these patients are inherently linked to the medications administered, and therefore their costs should be considered. Despite this, the analysis was undertaken to assess the results if amlodipine had been added to the treatment regimens using a truly incremental design.

A final scenario analysis was performed to compare the rate of events and procedures in the amlodipine cohort to that in the subset of patients in the placebo arm who were on concomitant calcium channel blockers (CCBs). As the event rate was higher among this subset of CCB users, the subsequent total expected cost per patient was, similarly, higher by approximately 10%, suggesting that amlodipine compares favourably with other CCBs in terms of event rates and costs. This analysis inherently favours the amlodipine cohort for a number of reasons, and therefore should be interpreted carefully. Specifically, it is likely that the average time on CCB therapy was lower in the subgroup of placebo patients since its use was not part of the drug treatment protocol for the study and is likely to have been undertaken on an as-needed basis. This may result in selection bias since the subset of patients in the placebo arm who required CCBs may have had more severe symptoms.

Limitations

A number of limitations warrant further discussion. In particular, the PREVENT study design did not accommodate the collection of economic data. Therefore, assumptions were made regarding costs and may not be a completely accurate reflection of the actual events. Furthermore, resource consumption related to outpatient follow-up care was estimated based on physician opinion.

Another notable limitation concerns the exclusion of hospitalisations that were not CVD-related. The base-case analysis includes only costs related to CVD and related illness. However, during the trial nearly 400 non-CVD hospitalisations occurred in the 825 trial participants and the amlodipine patients experienced approximately 30 more non-CVD hospitalisations over the course of the three-year study period. It was not possible to include these in the economic portion of the analysis.

Additional limitations include the generalisability of the clinical results in the US and Canada to CAD patients in the UK. The effect of this limitation was somewhat mitigated by the adjustments allowing for the reduced likelihood of performing interventional procedures and the increased prevalence of coronary artery disease in the UK.

Conclusion

Amlodipine patients experienced fewer hospitalisations for unstable angina, CABGs, PTCAs, CHF and MIs than placebo patients. This was attainable, over a three-year period, through an estimated cost investment of £58 per patient. This amounts to a cost of £331.67 per CVD hospitalisation avoided.

Several studies have evaluated the relationship between cardiovascular therapies, their effect on clinical outcomes, and how much more they can cost while still remaining economically desirable. Eisenstein *et al* designed a decision model to predict the six-month cumulative cost savings and increased life

Key messages

- PREVENT showed that amlodipine use reduced the frequency of hospitalisations for unstable angina and coronary revascularisations
- The expected cost per patient over the three-year trial period was £58.15 more for amlodipine patients
- This amounts to a cost of £331.67 per cardiovascular hospitalisation avoided

expectancy that could be associated with new therapies for patients with non-ST elevation acute coronary syndrome.[11] It was found that new therapies costing up to US$ 2,000 per episode that reduced six-month death, non-fatal MI and revascularisation by 3% were cost-effective by current standards.

Chambers *et al* performed a study to evaluate the cost-effectiveness of antiplatelet therapies in preventing recurrent stroke from the perspective of the UK health and social services. The model predicted that, over five years, a co-formulation of aspirin and dipyridamole prevented 29 more strokes over aspirin alone per 1,000 patients at an additional cost of £1,900 per stoke averted.[12]

Coronary artery disease is a life-threatening condition that requires continuous long-term medical management and often necessitates costly revascularisation techniques and repeated hospitalisations. Upon diagnosis, it is critical that measures are taken to impede the progression of the disease. A recent review by Brown and colleagues demonstrated the importance of non-surgical disease prevention strategies in adults with CAD.[13] Ideally, non-invasive treatment approaches would minimise future CVD-related events and the need for invasive surgeries.

The results of this pharmacoeconomic analysis demonstrate that the use of amlodipine resulted in fewer hospitalisations and the need for fewer invasive surgical procedures in the short and long term at a modest incremental cost. The incremental cost-effectiveness ratio as determined through this analysis compares favourably with the cost-effectiveness of other currently accepted interventions.

Acknowledgement

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Editors' note

Part 1 of this article 'Amlodipine treatment in patients undergoing PTCA in the UK: a cost-effectiveness analysis' was published last month (*Br J Cardiol* 2002;**9**:31-6).

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