Amlodipine treatment in patients undergoing PTCA in the UK: a cost-effectiveness analysis

JOHN J DOYLE, ERIK THAULOW, BJORN JORGENSEN, ROMAN CASCIANO, JULIAN CASCIANO, ZOE KOPP, NICK MARCHANT, RENEE KIM

Abstract

The objective of this analysis was to assess the health economic outcomes of treating patients undergoing percutaneous transluminal coronary angioplasty (PTCA) with amlodipine over a four-month time period in the UK. The total expected costs were determined and compared for patients using amlodipine versus those on placebo following an initial angioplasty. A decision tree model was constructed to estimate these total expected costs. Clinical data for the model were obtained from the Coronary Angioplasty Amlodipine Restenosis Study (CAPARES). Clinical outcomes in the model included myocardial infarction (MI), repeat PTCA, coronary artery bypass grafting (CABG) and all-cause mortality. Resource usage and economic data for the model were produced through the use of a modified Delphi panel and various economic literature and databases. The adjunctive use of amlodipine with PTCA decreased the rate of all adverse clinical outcomes by 9.4%. This improved clinical outcome led to a decrease in overall four-month costs per patient using amlodipine of £204. The total expected cost per patient using amlodipine was £3,833 and the total expected cost per patient not using amlodipine was £4,037.

Key words: costs, angioplasty, amlodipine, clinical outcomes.

The Analytica Group, 475 Park Avenue South, New York, NY 10016, US.
John J Doyle, Vice President
Roman Casciano, Managing Director
Julian Casciano, Vice President
Renee Kim, Senior Analyst

University Hospital Oslo, Rikshospitalet, 0027 Oslo, Norway.
Erik Thaulow, Head Section Congenital Heart Disease

Medisinsk avdeling, Baerum Sykehus, Postboks 34, 1306 Baerum Postterminal, Norway.
Bjorn Jorgensen, MD, PhD

Pfizer Inc, 235 East 42nd Street - 219/5/44, New York, NY 10017-5755, US.
Zoe Kopp, Senior Manager, Outcomes Research

Pfizer Ltd, Walton Vales, Dorking Road, Tadworth, Surrey, KT20 7NT, UK.
Nick Marchant, Outcomes Research Manager

Correspondence to: Mr Roman Casciano
(email: rcasciano@theanalyticagroup.com)

Introduction

In the United Kingdom (UK), the use of angioplasty increased by an average of 39% per year between 1985 and 1993.[1] Approximately 175 percutaneous transluminal coronary angioplasty (PTCA) procedures per million population were performed in 1992 and, by 1998, this number had increased to about 425 procedures per million population.[2] A percutaneous coronary intervention followed one out of five angiograms.[2] Although the success rate of the procedure itself is relatively high initially, PTCA can lead to adverse clinical outcomes and the need for revascularisation. A 1994 study by Hamm *et al* found that further interventions were necessary within one year of follow-up in 44% of PTCA patients.[3] Restenosis is estimated to occur in 20-50% of patients, with a peak incidence between one and four months after PTCA.[4-6] It has been reported that acute ischaemic complications alone can increase initial hospitalisation costs of PTCA by 150-400%.[7] In addition, any potential cost advantages associated with an initial PTCA are often offset by costs relating to subsequent revascularisation procedures and in-patient stays.[8] While advances in techniques have improved prognoses, there remains a need for greater understanding of more cost-effective interventions.

Calcium channel blockers inhibit platelet aggregation and reduce the production of platelet-derived growth factor which, in turn, may have the clinical advantage of reducing the incidence of complications relating to initial angioplasty.[9-13] In the recently published Coronary Angioplasty Amlodipine Restenosis Study (CAPARES), there was no significant angiographic evidence that amlodipine usage reduced mean loss in minimal lumen diameter, a measure of restenosis. However, use of amlodipine before and after PTCA was associated with a significant reduction in the incidence of composite major adverse clinical events (defined as death, myocardial infarction, CABG surgery or repeat PTCA).[14] Therefore, amlodipine may have potential health economic benefit through a substantial reduction in hospitalisations and costs associated with repeat revascularisations and complications of initial PTCA.

The objective of this analysis was to utilise the clinical findings of CAPARES to evaluate the health economic outcomes associated with using amlodipine in patients undergoing PTCA in the UK. Angiographic end points were evaluated in the CAPARES study but not in our economic analysis since clinical end points are the most relevant for an economic study. A decision tree model was developed to show the impact of amlodipine administration on the risk of myocardial infarction (MI), repeat PTCA,

coronary artery bypass grafting (CABG) and subsequent total health care costs.

Methods

A decision tree model was developed to evaluate the economic impact of the clinical outcomes for patients who used amlodipine with PTCA versus those who did not. Total expected costs were determined and compared for each of the two cohorts over a four-month period from the perspective of the UK National Health Service (NHS). Clinical outcome data in the decision tree model were obtained from the CAPARES trial and cost data were evaluated for each clinical outcome to perform the economic modelling. Clinical outcomes consisted of myocardial infarction (MI), CABG, repeat PTCA and all-cause mortality.

The CAPARES trial was conducted to investigate the effect of amlodipine on restenosis and clinical outcomes in patients undergoing PTCA. The prospective double-blind trial selected 635 patients from centres in Canada and Norway. These patients were randomised to 10 mg amlodipine (n=318) or placebo (n=317). Patients were started on 5 mg amlodipine and increased to 10 mg after one week. Drug treatment began two weeks prior to PTCA and ended four months after PTCA. Angioplasty was performed in 585 patients (92.1%), of whom 291 were in the amlodipine group and 294 in the placebo group. Only the clinical outcomes of these 585 patients were included in the decision tree model.

Since the study did not provide economic data, we performed an analysis to determine the cost of each of the outcomes in CAPARES for use in our economic model. In-patient costs were obtained from the 1999 National Schedule of Reference Costs of the NHS[15] and made up the majority of costs. The out-patient costs were also evaluated for a four-month period by creating a master list of resources using a modified Delphi panel approach. Five cardiology experts from the UK were questioned to establish a consensus on the prevailing clinical management of the relevant outcomes and the type and frequency of out-patient healthcare resources consumed during the course of treatment and follow-up care for MI, PTCA and CABG. Average values from the individual responses were used to determine total resource consumption per patient. Physicians were surveyed and follow-up questions were employed when necessary.

Costs were then assigned to each resource to estimate the total cost of each clinical outcome in the decision tree model. Three hospitals were surveyed for the unit costs of physician visits, laboratory tests, treatment costs and rehabilitative care.[16] Drug costs were obtained from the British National Formulary 37.[17] In addition, estimates of the incremental cost associated with multiple revascularisation procedures within a single hospitalisation were obtained from the RITA trial.[8] We accounted for differences between events which occurred during the initial revascularisation procedure and events which occurred post-discharge since these costs would vary. The results are presented in table 1.

Table 1. Cost breakdowns of clinical outcomes for PTCA, CABG and MI

PTCA		
In-patient costs[1,4]		
Total PTCA in-patient cost		£2,673.00
Total urgent PTCA in-patient cost		£2,450.13
Out-patient costs (four months)		
Lab tests[2]		£242.22
Physician visits[2]		£178.00
Drugs[3]		£296.12
	Total out-patient cost	£716.34
CABG		
In-patient costs[1,4]		
Total CABG in-patient cost		£6,105.00
Total urgent CABG in-patient cost		£3,137.58
Out-patient costs (four months)		
Lab tests[2]		£206.23
Physician visits[2]		£277.50
Long-term care[2]		£805.00
Drugs[3]		£198.30
	Total out-patient cost	£1,487.04
MI		
In-patient costs[1,4]		
Total MI in-patient cost		£1,285.00
Total urgent MI in-patient cost		£809.87
Out-patient costs (four months)		
Lab tests[2]		£586.48
Physician visits[2]		£272.50
Long-term care[2]		£153.60
Drugs[3]		£468.20
	Total out-patient cost	£1,480.78

Key: 1. The NHS 1999 National Schedule of Reference Costs[15]
2. Cost data from health economists at the following three hospitals:
   a. The Princess Margaret Hospital (public, Berkshire)
   b. The Cromwell Hospital (private, London)
   c. The Brompton Hospital (public, London)
3. British National Formulary 37[17]
4. Incremental cost for multiple procedures from RITA trial[8]

Results

Total in-patient costs were highest for CABG (£6,105) and lowest for MI (£1,285) (table 1). Patients who had either an MI or a CABG had the highest follow-up care costs, at £1,481 and £1,487 respectively. The highest cost patients were those who underwent CABG in addition to their initial PTCA, especially if CABG was performed after hospital discharge.

In the CAPARES clinical trial, the use of amlodipine in patients who underwent PTCA significantly reduced the incidence of composite major adverse clinical events such as repeat PTCA, CABG, MI and death. In the placebo cohort, 13.6% of patients experienced at least one adverse clinical outcome compared to 6.9% of patients in the amlodipine cohort (table 2). Among placebo patients, 3.7% had an MI, 7.8% had a repeat PTCA, 4.4% had a CABG and 0.3% died. Among amlodipine patients, 1.7% had an MI, 3.1% had a repeat PTCA, 1.7% had a CABG and 0.3% died.

Some of the placebo patients experienced more than one

Table 2. Rates of clinical end points in the CAPARES trial[14]

	Amlodipine group (n=291)	Placebo group (n=294)	p value
Events			
Death	0.3% (1)	0.3% (1)	0.99
MI	1.7% (5)	3.7% (11)	0.13
CABG	1.7% (5)	4.4% (13)	0.058
Repeat PTCA	3.1% (9)	7.8% (23)	0.011
Composite end points	6.9% (20)	13.6% (40)	0.007
All end points	6.9% (20)	16.3% (48)	

adverse clinical outcome (table 2) which explains why the rate of composite end points differs from the rate of all end points for placebo patients. Composite event rates, in which only the first event is counted for each patient, were not used in the base-case decision tree analysis. Instead, the rates used in the decision tree analysis reflected the rates of each event or procedure independent of one another (16.3% for the placebo group and 6.9% for the amlodipine group). While composite end points are often employed to report clinical data, economic models require complete accounting of events in order to measure costs accurately, therefore composite rates are not appropriate. To evaluate the impact of our chosen analytical approach, we performed a secondary analysis using only the composite end point rates.

Once each branch of the decision tree model had been assigned a cost and the probabilities of each clinical outcome from the CAPARES trial had been incorporated into the model, it was found that, over four months, patients who used amlodipine with PTCA had a lower total cost than patients who did not use amlodipine with PTCA. The decision trees in figures 1 and 2 represent the probabilities and costs associated with each possible combination of events experienced by both treatment arms. Expected cost is the weighted average cost of all possible combinations, including the cost of the initial PTCA procedure. The total expected cost per patient in the amlodipine cohort was estimated at £3,832.82 (figure 1) while the total expected cost per patient in the placebo cohort was estimated at £4,036.91 (figure 2). This translated into a cost difference of £204.09 per patient over four months.

A large portion of the cost savings generated in the amlodipine arm arose because smaller numbers of subjects required repeated interventions. Fewer patients in the amlodipine arm needed additional revascularisation, either PTCA or CABG, compared with the placebo arm (4.8% vs 12.2%).

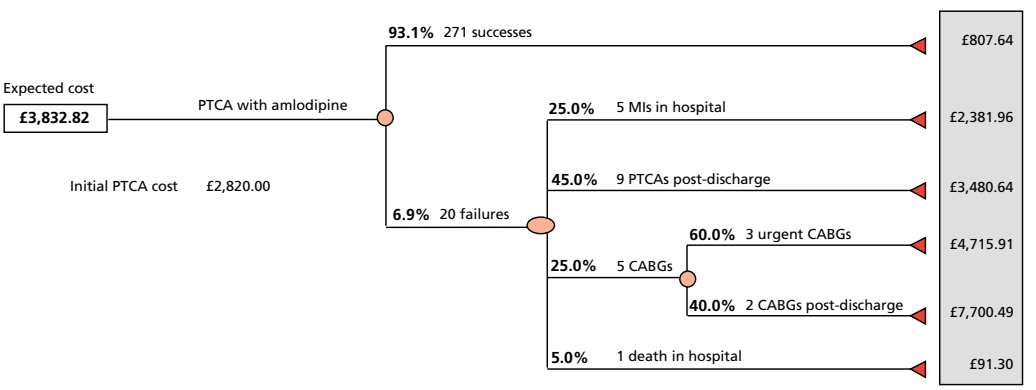
A secondary analysis was performed under the conservative assumption that patients with multiple events had experienced these events during the same hospital stay. Among CAPARES subjects, more than one event may have occurred during a single hospitalisation and so, from a cost perspective, they may not be mutually exclusive. To account for this in the most conservative fashion, and to avoid any possibility of double-counting costs, it was assumed that patients who experienced more than one event would only incur the cost of a single event. For the amlodipine arm, the results remain the same since there were 20 events in 20 patients. For the placebo group, 40 patients experienced 48 events. When it was assumed that each of the 40 patients incurred only the cost of one event, the overall expected cost of a placebo patient was reduced to £3,953 from £4,037 per patient in the base-case analysis: the cost saved per patient was reduced from £204 in the base-case analysis to £121.

Sensitivity analyses

Both univariate and multivariate sensitivity analyses were performed on key variables in the model in order to determine whether the rank order of the results would change as a result of varying parameter values.

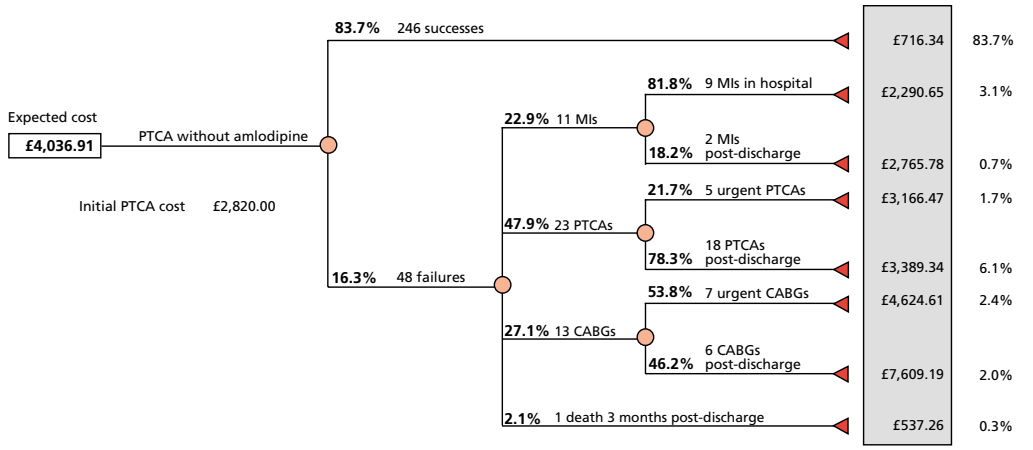
In the univariate analysis, a range of estimates was evaluated for in-patient medical costs and PTCA success rates. Varying in-patient costs by +/-20% did not result in a change in the rank-

Figure 1. Decision tree model for amlodipine cohort



Key: PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; CABG = coronary artery bypass grafting

Figure 2. Decision tree model for placebo cohort



Key: PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; CABG = coronary artery bypass grafting

order of the results. However, the model was sensitive to the relative success rate of PTCAs for amlodipine versus placebo. A 6.7% increase in the rate of adverse clinical outcomes of PTCAs with amlodipine (86.4% success rate and 13.6% failure rate for amlodipine cohort) resulted in a break-even of total expected costs between the two cohorts.

Multivariate analysis revealed that the model was robust when multiple parameters were varied simultaneously. Probabilities of an adverse clinical event were varied randomly within the 95% confidence interval, based on a normal distribution. Costs of clinical outcomes 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 iterations yielded a mean value of £3,833.87 with a standard deviation of £168.17. For the cost per patient in the placebo group, 10 000 iterations yielded a mean value of £4,035.36 with a standard deviation of £175.17. Results from this analysis indicated that the model was relatively insensitive to the varied parameters and did not substantially affect the total expected costs or the rank-order of the results.

Discussion

The adjunctive use of amlodipine with PTCA decreased the incidence of adverse clinical events, which led to a reduction in the four-month total expected cost for patients using amlodipine versus those not using amlodipine. Most of the cost savings were attributable to fewer subjects in the amlodipine treatment group undergoing costly revascularisation procedures compared with subjects in the placebo group.

There were several limitations inherent in this analysis. First, the clinical data utilised in this analysis were derived from a trial that included patients from Norway and Canada. Therefore, the clinical data may not be entirely generalisable to the UK population.

Second, only direct costs were included in the analysis. We did not consider here indirect costs relating to lost time and productivity.

Third, neither the clinical trial nor the economic model addressed quality of life issues, which are important outcome measures after an intervention. After initial PTCA, the amlodipine group had significantly fewer reinterventions compared to the placebo group. Further studies should be undertaken to quantify the benefits that these lower revascularisation rates have in terms of quality of life.

Fourth, the CAPARES trial did not evaluate patients with stents. Over the years, the practice of coronary stenting with PTCA has become standard as a result of the improvements in thrombosis and restenosis rates which accompany their usage.

Lastly, in order to mirror the duration of the clinical trial, the time frame chosen for the economic model was only four months. The time horizon for the model was not extended beyond the length of the clinical trial because it was uncertain whether the clinical benefits observed in the four-month clinical trial would persist further.

Amlodipine has been demonstrated to decrease the number of expensive repeat procedures needed. This translates into a reduction in medical risks and an overall cost saving for patients treated with PTCA. The NHS and healthcare providers in the UK should consider this pharmacoeconomic evidence in developing and promoting cost-effective treatments for coronary artery disease in the UK.

Acknowledgement

The study was sponsored by Pfizer Inc.

Editors' note

This article is the first of two looking at the cost-effectiveness of amlodipine treatment. Its costs in patients with coronary artery

Key messages

- In the CAPARES clinical trial, use of amlodipine in patients undergoing PTCA reduced major adverse clinical events
- This led to a reduction in the four-month total expected cost for patients using amlodipine
- Most of the cost savings were attributable to fewer revascularisations in the amlodipine group

disease in the UK will be considered in a future issue of the journal.

References

1. Robinson M, Manning R, Petticrew M, Rice N, Sculpher M, Sheldon T. Impact of national health care policies on trends in the use of technologies for heart attack care: UK and international comparisons. *Ann Meet Int Soc Technol Assess Health Care* 1999;**15**:63.
2. Boersma H, Doornbos G. Bloemberg BPM, Wood DA, Kromhout D, Simons ML (eds). *Cardiovascular diseases in Europe. European registries of cardiovascular diseases and patient management*. Sophia Antipolis: European Society of Cardiology, 1999.
3. Hamm C, Reimers J, Ischinger T *et al*. A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multi-vessel coronary disease. *N Engl J Med* 1994;**331**:1037-43.
4. Wong JB, Sonnenberg FA, Salem DN, Pauker SG. Myocardial revascularization for chronic stable angina: analysis of the role of percutaneous transluminal coronary angioplasty based on data available in 1989. *Ann Intern Med* 1994;**113**: 852-71.
5. Holmes DR, Vlietstra RE, Smith HC *et al*. Restenosis after percutaneous transluminal coronary angioplasty: a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;**53**:77C-81C.
6. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, DeFeyter PI, Van Den Brand M. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. *Circulation* 1988;**77**:361-71.
7. Dunn CJ, Foster RH. Abciximab: a pharmacoeconomic review. *Pharmacoeconomics* 1999;**16**(6):711-38.
8. Soulpher MJ, Seed P, Hamilton RA *et al*. Health service costs of coronary angioplasty and coronary artery bypass surgery: the RITA trial. *Lancet* 1994;**344**:927-30.
9. Greer IA, Walker JJ, McLaren M, Calder AA, Forbes CD. Inhibition of whole blood platelet aggregation by nicardipine, and synergism with prostacyclin *in vitro*. *Thromb Res* 1986;**41**:509-18.
10. Han P, Boatwright C, Ardlie NG. Effect of the calcium-entry blocking agent nifedipine on activation of human platelets and comparison with verapamil. *Throm Haemost* 1983;**50**:513-7.
11. Uehara S, Handa H, Hirayama A. Effects of the calcium antagonist nifedipine on thromboxane B2 level platelet aggregation in hypertensive patients. *Arzneimittelforschung* 1986;**36**:1687-9.
12. Jackson CL, Bush RC, Bowyer DE. Inhibitory effect of calcium antagonists on balloon catheter-induced arterial smooth muscle cell proliferation and lesion size. *Atherosclerosis* 1988;**69**:115-22.
13. Nomoto A, Mutoh S, Hagihara H, Yamaguchi I. Smooth muscle migration induced by inflammatory cell products and its inhibition by a potent calcium antagonist, nilvadipine. *Atherosclerosis* 1988;**72**:213-9.
14. Jorgensen B, Simonsen S, Endresen K *et al*. Restenosis and clinical outcome in patients treated with amlodipine after angioplasty: results from the coronary angioplasty amlodipine restenosis study (CAPARES). *J Am Coll Cardiol* 2000;**35**:592-9.
15. The New NHS National Schedule of Reference Costs, 1999.
16. Royal Brompton and Harefield NHS Trust data, 1999, The Princess Margaret Hospital, The Cromwell Hospital (obtained from health economists).
17. British National Formulary 37. London: British Medical Association, 1999.