An economic evaluation of valsartan for post-MI patients in the UK who are not suitable for treatment with ACE inhibitors

Matthew Taylor[1] Ph.D., Paul A Scuffham[2] Ph.D., Stephen Chaplin[1] B.Sc., Natalie L Papo M.Sc.[3]

1 University of York, York Health Economics Consortium, York, UK

2 Griffith University, School of Medicine, Brisbane, Australia

3 Novartis Pharmaceuticals, London, UK

Corresponding Author: Matthew Taylor, University of York, York Health Economics Consortium, Level 2, Market Square York YO10 5NH, UK

Tel: +44 1904 433631

F: +44 1904 433628

Email: mt25@york.ac.uk

Source of financial support: Novartis Pharmaceuticals for health economics consultancy in the development of this study.

Keywords: cardiovascular disease, stroke, heart failure, economic, model

Running Title: Economic evaluation of valsartan

Abstract [First-level Header]

Objectives The overall objective of this study was to estimate the costs and outcomes associated with treatment with valsartan for post-myocardial infarction (post-MI) patients with left ventricular systolic dysfunction, heart failure, or both, who are not suitable for treatment with ACE inhibitors, compared with placebo.

Methods: Using data drawn from the VALIANT trial and other trials, a Markov model was developed to predict the future health pathways, resource use and costs for patients who have recently experienced a myocardial infarction (MI). Patients received either valsartan (mean dose 247mg) or placebo. Cost data were drawn from national databases and published literature, whilst health outcome utility weights were derived from existing studies. Patient outcomes were modelled for ten years, and incremental cost-effective ratios (ICERs) were calculated for valsartan compared to placebo.

Results: Over a period of ten years, a cohort of 1,000 patients treated with valsartan experienced 147 fewer cardiovascular deaths, 37 fewer non-fatal MIs and 95 fewer cases of heart failure than a cohort who received placebo. The incremental cost of valsartan, compared to placebo, was £2,680 per patient, whilst the incremental effectiveness of valsartan was 0.5021 QALYs gained per patient. Therefore, the incremental cost per QALY for treatment with valsartan was £5,338. When analysis was undertaken using life-years rather than QALYs, the cost per life-year gained was £4,672.

Conclusions: For patients who are not suitable for treatment with ACE inhibitors, valsartan is a viable and cost-effective treatment for their management following a myocardial infarction.

Introduction [FIRST-LEVEL HEADER]

Myocardial infarction (MI) has severe consequences for both the patient and the health care system [1-5]. Valsartan is the only angiotensin II antagonist licensed for the management of post-MI patients with left ventricular systolic dysfunction, heart failure, or both [6]. Whilst angiotensin-converting enzyme (ACE) inhibitors are recommended as standard therapy for such patients, intolerability (e.g. cough) [4] and non-adherence [6; 7] are common problems. Therefore, an alternative is required to minimise further cardiovascular morbidity and mortality.

The overall objective of this cost-utility study was to estimate the costs and outcomes associated with treatment with valsartan for post-MI patients with left ventricular systolic dysfunction and/or heart failure who are not suitable for treatment with ACE inhibitors (i.e. those for whom ACE inhibitors had caused intolerable adverse events, or for whom adherence was affected by adverse events). Because these patients are not suitable for treatment with ACE inhibitors, the comparator was placebo (i.e. no ACE or valsartan treatment).

Methods [FIRST-LEVEL HEADER]

A Markov model was constructed, using Microsoft Excel 2000 [8]. A Markov model is a type of quantitative model that involves a specific set of mutually exclusive and exhaustive health states representing the natural course of a disease. Markov models are a useful approach for estimating the future health pathways, outcomes and costs of patients. The model was constructed to estimate the costs and outcomes following an initial MI for two cohorts of patients who require medical management and are not suitable for treatment with ACE inhibitors. Thus, the model includes one cohort of patients treated with valsartan (mean dose of 247mg ± 105mg daily, as in the Valsartan in Acute Myocardial Infarction (VALIANT) clinical trial [6]), and a second cohort who received placebo. Patients began treatment between zero and ten days following their MI.

The (VALIANT) trial recently demonstrated the clinical effectiveness efficacy of valsartan [6] in post-MI patients with evidence of left sided heart failure. The VALIANT trial provided a randomised, double-blinded comparison of valsartan with captopril (an ACE inhibitor) in more

than 14,000 patients (randomised to three treatment arms), who were followed for an average of 24.7 months. Other trials have compared ACE inhibitors against placebo [9-12]. Mortality rates and other clinical outcomes were estimated for each treatment option (i.e. valsartan and placebo), using trial data. The trial data were combined with resource use and unit cost data to estimate the relative effects of valsartan and placebo for the treatment of post-MI patients who are not suitable for treatment with ACE inhibitors.

The time horizon used for the model was ten years. This allowed for any variations in mortality to be captured, as well as predicting the true long-term costs associated with each treatment. The time horizon was varied in the sensitivity analysis to see what impact this may have. In the UK, the majority of costs for post-MI treatment are borne by the National Health Service (NHS). Therefore, the perspective of the NHS was selected for this study.

The Markov Model [First-level Header]

The Markov model for this study consisted of five distinct health states:

- No complications (following first MI);
- Post-heart failure;
- Post-stroke;
- Post-subsequent MI;
- Death.

All patients entered the model after their first MI (i.e. after diagnosis and appropriate management of the first MI) and moved to different health states, depending upon the likelihood of progression (see transition probabilities section). For example, a patient may have begun with no complications following an initial MI, and may have remained in that state for approximately two years. After two years, the patient may have suffered a stroke. In this case, the patient would move to the post-stroke state, until a further change occurred, or until the ten years were over. Note that patients who died remain in the death state for the remainder of the model. Figure 1 shows the structure of the Markov model.

[Fig 1about here]

For the purposes of this analysis, it was conservatively assumed that patients who had successive events would maintain the worst state. For example, a post-stroke patient who suffered heart failure would remain in the post-stroke state, because the symptoms following stroke are more severe than those following heart failure. The list of health states is shown in Table 3.

Cycles in the model lasted for three months. Therefore, a patient who survived for the full ten years experienced a total of forty cycles. A three-month cycle was selected because this allows the model to incorporate the fact that mortality rates are significantly higher in the first three months following an MI than in subsequent months.

Transition Rates and Resource Use [Second-level Header]

For valsartan, the events rates were drawn from the VALIANT trial for valsartan patients [6]. For placebo, the rates were drawn from a meta-analysis [12] of the AIRE [9], SAVE [10] and TRACE [11] trials for patients treated with placebo. All rates are shown in table 1. The VALIANT trial compared the efficacy of valsartan versus the ACE inhibitor captopril. The AIRE, SAVE and TRACE trials compared the efficacy of 3 different ACE inhibitors versus placebo after an acute MI, i.e. in a population similar to that in the VALIANT trial, with recent MI and evidence of impaired left ventricular function).. The AIRE, SAVE and TRACE trials were synthesized in 2000 [12], and these overall event rates were used in the model.

Event rates for patients on placebo were calculated as a ratio of ACE inhibitor rates, as observed in the meta-analysis of the AIRE, SAVE and TRACE trials. In line with the VALIANT trial which showed that valsartan is as effective as captopril [6], it was assumed that the ratio for valsartan versus placebo was the same as that of ACE inhibitors against placebo. For example, the three-monthly risk of heart failure for placebo patients was 1.33 times that of ACE inhibitor patients (taken from the meta-analysis of those trials). Because the risk of admission for heart failure for valsartan patients in the VALIANT study was 1.3% in the first three months for valsartan patients, it was assumed that the risk for placebo patients was 1.73% (i.e. 1.33

multiplied by 1.3%). No patients who were included in the VALIANT trial were excluded from the economic analysis. Patients receiving valsartan who experienced adverse events (based on 'all discontinuation due to adverse events' rates observed in the VALIANT trial) were assumed to discontinue treatment. Thereafter, these patients were assumed to experience effectiveness equivalent to placebo therapy.

Because acute events are more likely to occur immediately following another event, rates were disaggregated into the three-month period after an event, and any subsequent three-month period. Mortality and morbidity rates were calculated using Kaplan-Meier curves from the VALIANT trial, and probabilities for three-month cycles were converted from trial rates (of 24.7 months) using the formula: $P_{3months} = 1-(1-P_{24.7months})^{3/24.7}$. Due to a lack of available data, it was not possible to correlate the frequency of events with the likelihood of further events.

[Tables 1 and 2 about here]

In order to estimate the costs associated with follow up for stroke, heart failure and MI patients, some assumptions based on expert clinical opinion about resource use were required. For example, it was assumed that, because of increased dependency and disability, patients who had experienced a stroke would have three times the resource use (other than revascularisation) of post-heart failure patients. Table 2 shows the annual resource use for these patients by number of visits per patient or proportion of patients undergoing procedure.

Health Outcomes [Second-level Header]

The summary outcome measure used in this study was the quality-adjusted life year (QALY). The QALY is a utility measurement, quantifying a patient's health-related quality of life (morbidity) and length of life (mortality). To calculate total QALYs, the utility values were multiplied by the duration in each health state throughout the time horizon of the model. Because the QALY accounts for both quality and quantity of life, it is superior to simple effectiveness measures such as event rates, which assign equal weight to all outcomes. For each health state in the model (i.e. no complications, post-heart failure, post-stroke and death), a utility weight was applied, in the range between 0 = dead and 1 = full health.

The utility weights were taken from existing literature (Table 3). The weights for no complications and heart failure were drawn from a 1993 study undertaken by Tsevat *et al*. [13], who used the time trade-off approach for utility elicitation. The quality of life associated with post-stroke was derived from a 2003 meta-analysis by Tengs [14], which pooled quality of life (QoL) data to offer analysts QoL estimates based on the entire stroke literature rather than just a single estimate. In addition, it was assumed that, for acute events such as MI, stroke and acute heart failure, the patient would experience seven days of extreme severe impairment to quality of life [15]. Therefore, it was assumed that patients experienced zero utility for a seven-day period after an acute event. This assumption was later tested in the sensitivity analysis.

[Table 3 about here]

In addition to QALYs, the total life-years gained for patients are also reported. Life-years gained are a useful guide to patients' survival rates, but do not account for variation in the quality of a patient's life.

Costs [Second-level Header]

The perspective of the cost-effectiveness analysis was the cost to the NHS. Because the VALIANT trial was multinational, resource use and other cost data would not necessarily be reflective of the UK setting. Therefore, in this study cost and resource data were drawn from national sources.

The NHS Reference Costs for 2005 were used for inpatient procedures and outpatient attendances [16]. Average costs were calculated using the health related group (HRG) code for non-fatal MI, stroke and heart failure. These costs were weighted to take into account the proportion of patients who received emergency and elective care. Table 4 includes the inpatient unit costs used in the model. Total costs were estimated using the predicted resource use for each state (from Table 2), multiplied by the unit costs (table 4). The unit costs used in the follow up calculations are also shown in Table 4. All costs are presented in 2008 prices and were inflated where necessary.

[Table 4 about here]

Because health outcomes and costs arising in the future tend to be valued less than those occurring now, the value of future outcomes were discounted. Both health outcomes and costs were discounted at a rate of 3.5% *per annum*, as recommended by the National Institute for Health and Clinical Excellence and the Scottish Medicines Consortium [17-19]. Discount rates were varied in the sensitivity analysis.

One-way sensitivity analyses were carried out in order to determine which parameters had the greatest impact on the model's findings. In most cases, ranges were selected by increasing or decreasing the base case value by 20%.

Results [FIRST-LEVEL HEADER]

Incremental Analysis [Second-level Header]

Table 5 shows the incremental results. Over a period of ten years, the valsartan cohort experienced 431 cardiovascular deaths per 1000 patients, compared to 578 in the placebo group. The valsartan group experienced 178 non-fatal MIs, 314 cases of heart failure and 48 strokes over ten years, compared with 215, 409 and 43 respectively in the placebo group.

In the base case analysis, the valsartan cohort cost an average of £8,878 per patient over the ten-year period. In comparison, the placebo cohort cost an average of £6,198 per patient over the same period (these costs reflect treatment for adverse events and other follow up costs). Therefore, the incremental cost of valsartan was £2,680 per patient. Patients in the valsartan group experienced a total of 5.021 QALYs per patient, compared to 4.519 QALYs in the placebo group. Therefore, 0.502 additional QALYs were gained over the ten years modelled.

The incremental cost per QALY gained for treatment with valsartan was, therefore, £5,338. When the analysis was undertaken using life-years rather than QALYs, the cost per life-year gained was £4,672.

[Table 5 about here]

One-Way Sensitivity Analysis [Second-level Header]

Table 6 shows the relative effects of various changes to key parameters used in the Markov model.

[Table 6 about here]

The utility weight applied to having no complications had a major impact on the model's findings. When the utility weight was increased to 1.00, the cost per QALY gained fell to £4,726. This is due to the increased benefits associated with valsartan which reduces the risk of complications. When the utility weight was decreased by 20% (to 0.70), the ICER increased to £6,624. The event rates for cardiovascular death were also key drivers in the model.

The model was robust to many factors, including the cost of events, the cost of follow ups, the quality of life associated with post-stroke and post-heart failure, and changes in the likelihood of patients discontinuing valsartan.

Probabilistic Sensitivity Analysis [Second-level Header]

Probabilistic sensitivity analysis (PSA) was undertaken to estimate the level of confidence around the model's cost-effectiveness outputs. Distributions were fitted to key model parameters, where data were available (see Tables 3 and 4). The outputs from the PSA show relatively little variation in the incremental costs and outcomes (see Figure 2). As such, the cost-effectiveness acceptability curve (Figure 3) shows that there is a high degree of confidence associated with valsartan being a cost-effective intervention.

Discussion [FIRST-LEVEL HEADER]

The cost-effectiveness estimate of valsartan following an MI in patients with evidence of left ventricular systolic dysfunction, heart failure, or both unsuitable for ACE inhibitors compared to placebo with a ten-year time horizon was £5338 per QALY. No other studies have undertaken a cost-effective analysis of treatments specifically for post-MI patients who are not suitable for treatment with ACE inhibitors. However, several studies have assessed the cost-effectiveness of ACE inhibitors, including Tsevat *et al*., who showed that the cost-effectiveness of captopril (compared to placebo) after MI ranged between $3,600 and $60,800 per QALY (US dollar, 1991 prices), depending on the age of the patient and the persistence of treatment benefits [20]. Martinez & Ball estimated that the cost-effectiveness of ramipril (compared to placebo) was around £300 per life-year gained (1993 prices) [21].

This economic evaluation used effectiveness data drawn directly from the VALIANT trial and disaggregated outcomes into five events (no complications, stroke, heart failure, subsequent MI and death). The proportion of patients in each state during the ten-year period can be estimated from the model. In the placebo group of the model, the survival rate for patients after ten years was 33.83%, compared with 42.85% in the valsartan group. The difference in mortality was apparent from the outset, with 85.09% of placebo patients surviving the first year, compared to 88.28% of valsartan patients. This was a key factor in the cost-effectiveness results, suggesting that both quality and quantity of life are improved by treatment with valsartan.

The VALIANT trial was undertaken on 14,703 patients from twenty-four different countries. There is no evidence that individual cases of MI in the UK are more severe than in other countries. Therefore, it is reasonable to assume that these findings are applicable to UK patients. Although effectiveness data from several countries were used, the economic model was populated with UK cost and resource use data.

This analysis is not without its limitations. Data were obtained from the published literature and therefore some assumptions were required. For example, effectiveness data for valsartan were drawn from the VALIANT trial [6], which undertook analysis on patients receiving valsartan, captopril, or both, and which excluded patients unsuitable for treatment with ACE inhibitors. On

the other hand, this cost-effectiveness analysis focused on patients who were unsuitable for treatment with ACE inhibitors. Therefore, it was necessary to assume that patients who are not suitable for ACE inhibitors would experience similar benefits of valsartan as patients who are suitable for ACE inhibitors. Expert opinion was used for some model inputs, where published data were not available. However, such use was based upon alternative data (e.g. a similar condition) and was tested in the sensitivity analysis.

The treatment effects were assumed to last for the duration of the model. However, it was also assumed that treatment (and, therefore, treatment cost) would continue throughout the model. If the effectiveness of treatment were to discontinue, then the patient could be assumed to stop treatment. As such, the incremental effectiveness *and* cost would be reduced by an equal proportion, since patients would switch to a treatment equivalent to that of the comparator group.

Other costs, such as nursing homes, were excluded from the analysis due to a lack of reliable resource use data. This assumption is likely to be conservative, since improved health outcomes would be more likely to be associated with reduced resource utilisation.

Conclusions [FIRST-LEVEL HEADER]

The estimated ICER for valsartan in this study is well within the bounds of cost-effectiveness acceptability implied by decision-making bodies. Furthermore, sensitivity analysis demonstrated that changes to key parameters did not increase the ICER significantly close to such thresholds. Therefore, for patients with evidence of with left ventricular systolic dysfunction, heart failure, or both who are not suitable for treatment with ACE inhibitors, valsartan is a viable and cost-effective treatment for their management following myocardial infarction.

References [First-level Header]

1. Dickson M Jacobzone S. Pharmaceutical use and expenditure for cardiovascular disease and stroke: a study of 12 OECD countries. OECD Health Working Paper. 2003;1:1-79

2. PRAIS-UK Investigators. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). Euro Heart J 2001;21:1450-7.

3. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Euro Heart J 2003;24:1601-10.

4. Fox KA, Goodman SG, Anderson FA, et al. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. Euro Heart J 2003;24:1414-24.

5. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variations in practice and outcome. Euro Heart J 2002;23:1177-89.

6. The VALIANT Investigators. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Disease, or Both. N Engl J Med 2003;349:1893-906.

7. Struthers A, Anderson G, MacFadyen R, et al. Non-adherence with ACE inhibitor treatment is common in heart failure and can be detected by routine serum ACE activity assays. Heart 1999;82:584-8.

8. Microsoft. Excel 2000. http://www.microsoft.com/uk/office/excel/. Date Accessed: 6 March 2008

9. The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669-77.

10. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821-8.

11. Kober L, Torp-Pedersen C, Carlsen J, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670-6.

12. Flather M, Yusuf S, Kober L, et al. Long-term ACE inhibitor therapy in patients with heart failure of left-ventricular dysfunction: A systematic overview of data from individual patients. Lancet 2000;355:1575-81.

13. Tsevat J, Goldman L, Soukup J, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993;13:161-5.

14. Tengs T Lin T. A meta-analysis of quality of life estimates for stroke. Pharmacoeconomics 2003;21:191-200.

15. Kuntz K, Tsevat J, Goldman L, Weinstein M. Cost-effectiveness of routine coronary angiography after acute myocardial infarction. Circulation 1996;94 957-65.

16. Department of Health. NHS Reference Costs 2004 2005;volume:page range. No page range or volume, since data were retrieved from the tables published online. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4105545 Last accessed 6 March 2008.

17. Scottish Medicines Consortium. Guidance to Manufacturers: Notes for the Completion of the New Product Assessment Form. 2004.

18. National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. http://www.nice.org.uk/page.aspx?o=201973. Date Accessed: 2 February. 2006.

19. HM Treasury. http://www.hm-treasury.gov.uk/. Date Accessed: 2 February 2006.

20. Tsevat J, Duke D, Goldman L, et al. Cost-effectiveness of captopril therapy after myocardial infarction. J Am Coll Cardiol 1995;26:914-19.

21. Martinez C Ball S. Cost-effectiveness of rampril therapy for patients with clinical evidence of heart failure after acute myocardial infarction. Brit J Clin Prac 1995;(Supp. 78):26-32.

22. Fox KA, Cokkinos DV, Deckers J, Keil U, et al. The ENACT Study: A pan-European survey of acute coronary syndromes. Euro Heart J 2000;21:1440-9.

23. BCIS Audit Returns 2001. http://www.bcis.org.uk/audit/oct02.html. Date Accessed: 11 November 2003.

24. Grover S, Coupal L, Zowall H, et al. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? Diabetes Care 2001;24:45-50.

25. Curtis L Netten A. Unit Costs of Health and Social Care 2005. 2005;

26. British Medical Association RPSoGB. British National Formulary 55. London: Royal Pharmaceutical Society of Great Britain, 2005.

Figure 1: The Markov Model

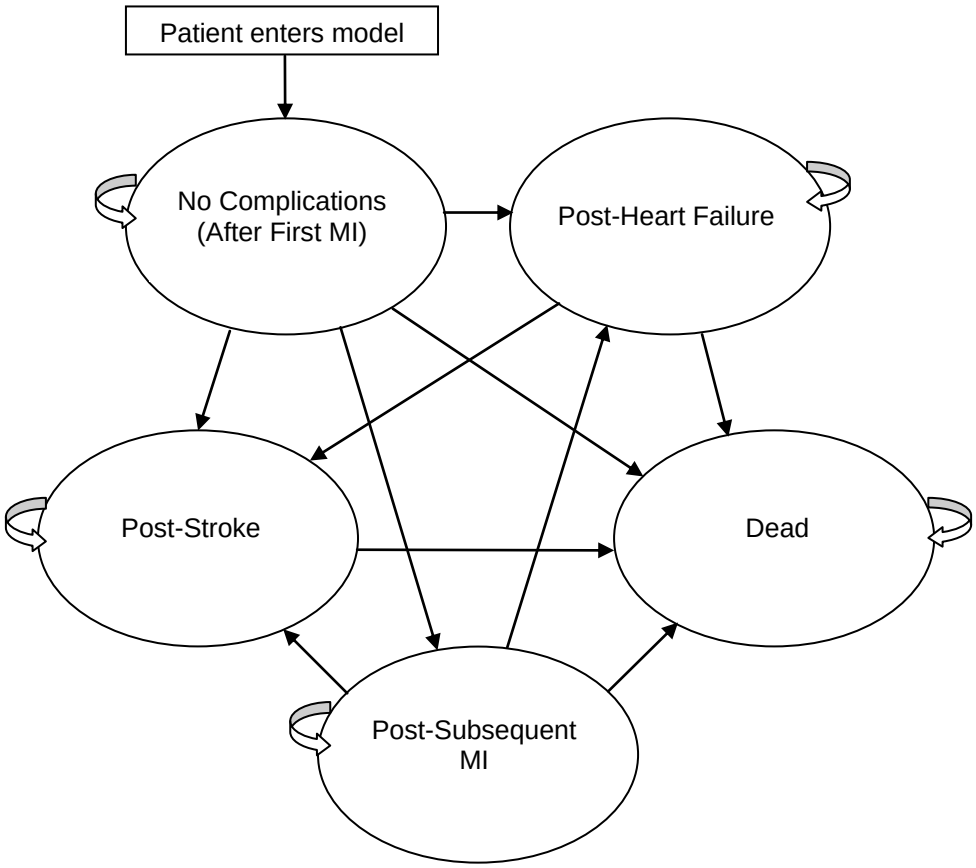

Figure 2: Cost-effectiveness scatter plot

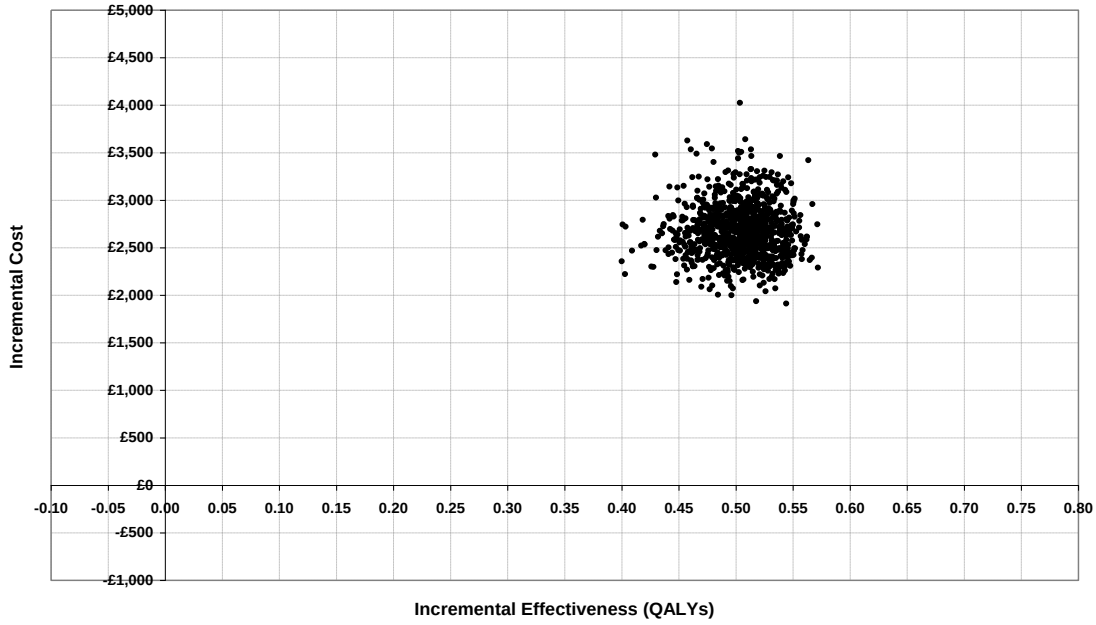

Figure 3: Cost-effectiveness acceptability curve

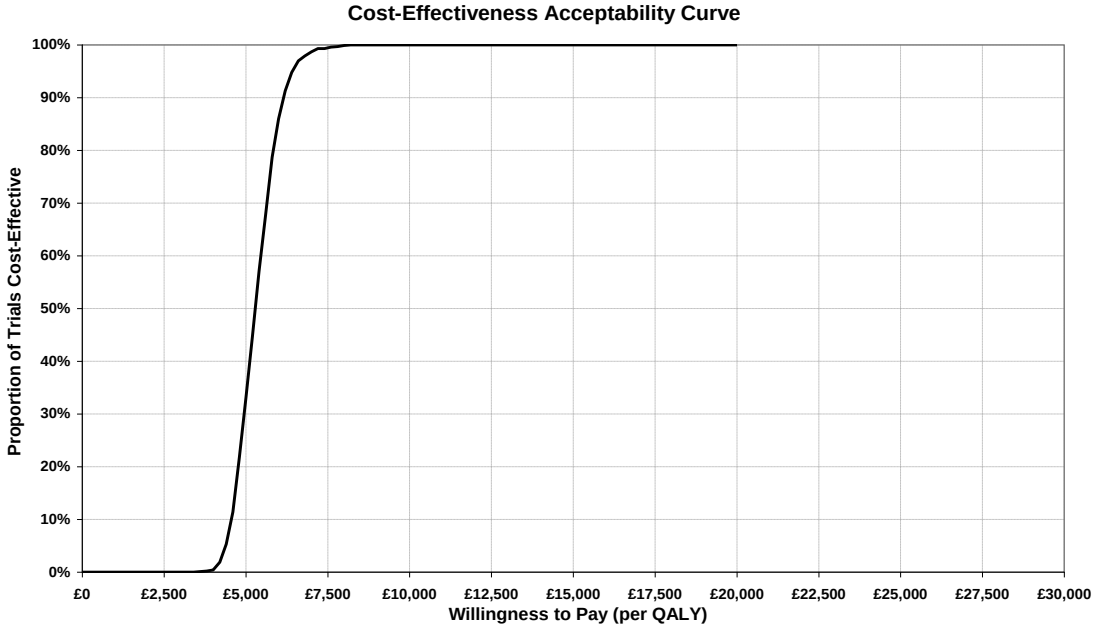

Table 1: Event rates used in the model (transition probabilities)

Event	First three months	Subsequent three month periods
Valsartan *		
Cardiovascular death	6.00%	1.58%
Other death	0.35%	0.35%
Non-fatal MI	0.73%	0.73%
Heart failure	1.30%	1.28%
Non-fatal stroke	0.20%	0.20%
Discontinue due to adverse events	2.90%	0.41%
Placebo †		
Cardiovascular death	7.77%	2.18%
Other death	0.35%	0.35%
Non-fatal MI	0.90%	0.90%
Heart failure	1.73%	1.71%
Non-fatal stroke	0.18%	0.18%

* Source: VALIANT trial [6]

† Source: Flather *et al*. [12], as a ratio of the VALIANT trial results [6].

Table 2: Annual resource use for follow up of patients

Resource	Post-MI *	Post-heart failure	Post-stroke †
Visits			
GP clinic visits	2	2 *	6
Cardiologist visits	1	1 *	3
Nurse visits	0	13 *	39
Investigations			
Exercise tolerance test ‡	90% of patients	90% of patients *	90% of patients x 3 times
Angiography	15% of patients	15% of patients *	15% of patients x 3 times
Revascularisation			
PCI §	9% of patients	9% of patients	9% of patients
CABG ‖	5% of patients	5% of patients	5% of patients

* Source: expert clinical opinion (Dr David Newby, Clinician and Senior Lecturer in Cardiology, University of Edinburgh, UK),.

† It was assumed that resource use for post-stroke patients was three times that of post-heart failure patients (see *).

‡ It was assumed that 10% of patients would not be suitable for the test (see *).

§ Source: [22].

‖ Source: [23].

GP = general practitioner

PCI = percutaneous coronary intervention

CABG = coronary artery bypass graft

Table 3: Utility weights for health states

Health State	Utility Weight	St dev
No complications following first or subsequent MI [13]	0.880	0.05
Post- stroke [14]	0.680	0.18
Post-heart failure [13]	0.840	0.10†
Death	0.000	
Acute events *		
Acute MI (disutility)	-0.0183	
Non-fatal stroke (disutility)	-0.0142	
Heart failure (disutility)	-0.0175	

* For acute events, disutility was calculated by applying a utility of zero for seven days. The weight for the remainder of the cycle would be equivalent to the non-acute equivalent.

† Assumption.

Table 4: Unit costs used in the model

Resource	Cost (2008 £)	St. dev
Single events *		
Cardiovascular death †	1,317.21	1,000#
Non-fatal MI	1,176.57	1,167
Stroke	2,275.47	1,677
Heart failure	1,535.521	734
Other death ‡ §	375.75	200 #
Follow up costs §		
GP visit	20.99	
Cardiologist visit	71.37	
Nurse visit	18.89	
Investigations		
Exercise tolerance test ‖	28.34	
Angiography *	390.44	
Revascularisation *		
PCI	3,015.42	
CABG	7,492.88	
Drug costs ¶		
Valsartan (3 months' treatment)	108.97	

* Source: NHS Reference Costs [16] unless stated otherwise.

† Source: Grover *et al*. [24], reflated to 2008 prices.

‡ Cost of other death included one ambulance journey and a 50-50% mix of A&E visit and GP home visit.

§ Source: Netten & Curtis [25].

‖ Calculated by multiplying the cost of a nurse visit by 1.5 (representing nurse time, plus other, i.e. equipment & analysis of results).

¶ Source: British National Formulary 55 [26], mean dose 247mg daily

\# assumption

Table 6: Incremental Results

	Valsartan	Placebo	Incremental
Cost	£8,878	£6198	£2,680
QALYs	5.021	4.519	0.502
Life years (LYs)	5.803	5.230	0.574
Incremental cost per QALY			£5,338
Incremental cost per LY			£4,672

Table 6: Sensitivity Analysis Results

Variable (base value)	Low parameter value	ICER (£)	High parameter value	ICER (£)
Base case scenario ICER	£5,338			
Costs				
Cardiovascular death (£1,317)	£659	5459	£1,976	5217
Non-fatal MI (£1,177)	£588	5357	£1765	5319
Stroke (£2,275)	£1138	5321	£3,413	5355
Heart failure (£1,536)	£768	5419	£2,303	5256
Other death (£376)	£188	5335	£564	5341
Post-MI follow up (£844)	£422	4793	£1,266	5882
Post-stroke follow up (£1,935)	£967	5269	£2,902	5407
Post-heart failure follow up (£1,076)	£537	5,428	£1,614	5248
Cost of valsartan (£109 per cycle)	£54	2990	£163	7685
QALY				
No complications (and post-MI) (0.88)	0.70	6624	1	4726
Post-non-fatal stroke (0.68)	0.54	5394	0.82	5283
Post-heart failure (0.84)	0.67	5167	1	5504
Event Rates * (1st 3 mths, later 3 mths)				
Valsartan				
Cardiovascular death (6.00%, 1.58%)	4.8%, 1.26%	3867	7.2%, 1.9%	10,426
Non-fatal MI (0.73%, 0.73%)	0.37%, 0.37%	5354	1.48%, 1.48%	5305
Heart failure (1.3%, 1.28%)	0.59%, 0.59%	5448	2.60%, 2.60%	5187
Non–fatal stroke (0.20%, 0.20%)	0.10%, 0.10%	5248	0.40%, 0.40%	5528
Discontinue due to adverse events (2.90 %, 0.41%)	1.45%, 0.20%	5309	5.80%, 0.82%	5397
Other				
Discount rate ‡ (3.5%)	0%	5127	6%	5494

* Both first three-month and subsequent three-month periods were increased / decreased by 20%

† Both costs and benefits were discounted at the same rates