Volume 12 • Number 4 • 2009
VALUE IN HEALTH

An Economic Evaluation of Valsartan for Post-MI Patients in the UK Who Are Not Suitable for Treatment with ACE Inhibitors

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ABSTRACT

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 angiotensin-converting enzyme (ACE) inhibitors, compared to placebo.
Methods: A Markov model, using data drawn from the Valsartan in Acute Myocardial Infarction (VALIANT) trial and other trials, was developed to predict the future health pathways, resource use, and costs for patients who have recently experienced an MI. Patients received either valsartan (mean dose 247 mg) or placebo. Cost data were drawn from national databases and published literature, although health outcome utility weights were derived from existing studies. Patient outcomes were modeled for 10 years, and incremental cost-effective ratios were calculated for valsartan compared with placebo.
Results: Over a period of 10 years, a cohort of 1000 patients treated with valsartan experienced 147 fewer cardiovascular deaths, 37 fewer nonfatal MIs, and 95 fewer cases of heart failure than a cohort who received placebo. The incremental cost of valsartan, compared with placebo, was £2680 per patient, although the incremental effectiveness of valsartan was 0.5021 quality-adjusted life-years (QALYs) gained per patient. Therefore, the incremental cost per QALY for treatment with valsartan was £5338. When analysis was undertaken using life-years rather than QALYs, the cost per life-year gained was £4672.
Conclusions: For patients who are not suitable for treatment with ACE inhibitors, valsartan is a viable and cost-effective treatment for their management after an MI.
Keywords: cardiovascular disease, economic, heart failure, model, stroke.

Introduction

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]. Although angiotensin-converting enzyme (ACE) inhibitors are recommended as standard therapy for such patients, intolerability (e.g., cough) [4] and nonadherence [6,7] are common problems. Therefore, an alternate is required to minimize 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

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 after 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 dosage of 247 mg ± 105 mg daily, as in the Valsartan in Acute Myocardial Infarction (VALIANT) clinical trial [6]) and a second cohort who received placebo. Patients began treatment between 0 and 10 days after their MI.

The VALIANT trial recently demonstrated the clinical effectiveness and efficacy of valsartan [6] in post-MI patients with evidence of left-sided heart failure. The VALIANT trial provided a randomized, double-blinded comparison of valsartan with captopril (an ACE inhibitor) in more than 14,000 patients (randomized 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 10 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.

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10.1111/j.1524-4733.2008.00494.x

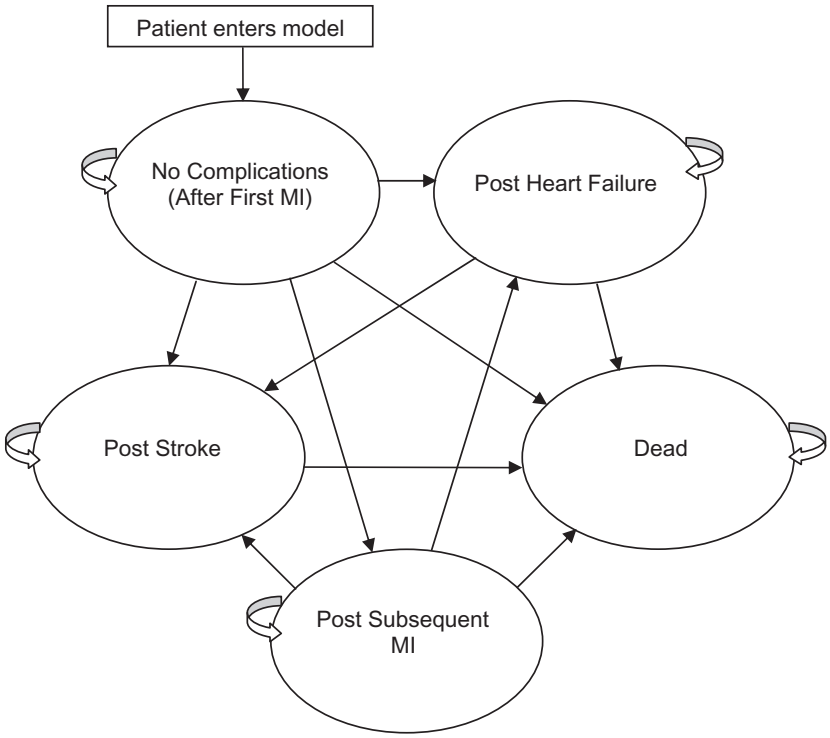

Figure 1 The Markov model. MI, mycardial infarction.

The Markov Model

The Markov model for this study consisted of five distinct health states: 1) no complications (after first MI); 2) postheart failure; 3) poststroke; 4) postsubsequent MI and 5) 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 after an initial MI and may have remained in that state for approximately 2 years. After 2 years, the patient may have suffered a stroke. In this case, the patient would move to the poststroke state, until a further change occurred, or until the 10 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.

For the purposes of this analysis, it was conservatively assumed that patients who had successive events would maintain the worst state. For example, a poststroke patient who suffered heart failure would remain in the poststroke state because the symptoms after stroke are more severe than those after heart failure. The list of health states is shown in Table 1.

Cycles in the model lasted for 3 months. Therefore, a patient who survived for the full 10 years experienced a total of 40 cycles. A 3-month cycle was selected because this allows the model to incorporate the fact that mortality rates are significantly higher in the first 3 months after an MI than in subsequent months.

Transition Rates and Resource Use

For valsartan, the event 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 [10], SAVE [9], and TRACE [11] trials for patients treated with placebo. All rates are shown in Table 2. The VALIANT trial compared the efficacy of valsartan versus the ACE inhibitor captopril. The AIRE, SAVE, and TRACE trials compared the efficacy of three 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 3-month 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 3

Table 1 Utility weights for health states

Health state	Utility weight	SD
No complications after first or subsequent MI [13]	0.880	0.05
Poststroke [14]	0.680	0.18
Postheart failure [13]	0.840	0.10*
Death	0.000	
Acute events†		
Acute MI (disutility)	–0.0183	
Nonfatal stroke (disutility)	–0.0142	
Heart failure (disutility)	–0.0175	

*Assumption.
†For acute events, disutility was calculated by applying a utility of zero for 7 days. The weight for the remainder of the cycle would be equivalent to the nonacute equivalent.
MI, myocardial infarction.

Table 2 Event rates used in the model (transition probabilities)

Event	First 3 months (%)	Subsequent 3-month periods (%)
Valsartan*		
Cardiovascular death	6.00	1.58
Other death	0.35	0.35
Nonfatal MI	0.73	0.73
Heart failure	1.30	1.28
Nonfatal 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
Nonfatal MI	0.90	0.90
Heart failure	1.73	1.71
Nonfatal stroke	0.18	0.18

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

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

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 dependence and disability, patients who had experienced a stroke would have three times the resource use (other than revascularization) of postheart failure patients. Table 3 shows the annual resource use for these patients by number of visits per patient or proportion of patients undergoing procedure.

Health Outcomes

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, postheart failure, poststroke, 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 1). 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 poststroke was derived from a 2003 meta-analysis by Tengs and Lin [14] who pooled quality-of-life data to offer analysts quality-of-life 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 7 days of extreme severe impairment to quality of life [15]. Therefore, it was assumed that patients experienced zero utility for a 7-day period after an acute event. This assumption was later tested in the sensitivity analysis.

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

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 code for nonfatal MI,

Table 3 Annual resource use for follow up of patients

Resource	Post-MI*	Postheart failure	Poststroke†
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 × 3
Angiography	15% of patients	15% of patients*	15% of patients × 3
Revascularization			
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 poststroke patients was three times that of postheart failure patients (see *).
‡It was assumed that 10% of patients would not be suitable for the test (see *).
§Source: [21].
‖Source: [22].
MI, myocardial infarction; GP, general practitioner; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 4 Unit costs used in the model

Resource	Cost (2008 £)	SD
Single events*		
Cardiovascular death†	1317.21	1000‡
Nonfatal MI	1176.57	1167
Stroke	2275.47	1677
Heart failure	1535.521	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	
Revascularization*		
PCI	3015.42	
CABG	7492.88	
Drug costs#		
Valsartan (3 months of treatment)	108.97	

*Source: NHS Reference Costs [16] unless stated otherwise.
†Source: Grover et al. [23], reflated to 2008 prices.
‡Assumption.
§Cost of other death included one ambulance journey and a 50% to 50% mix of A&E visit and GP home visit, respectively.
‖Source: Curtis and Netten [24].
¶Calculated by multiplying the cost of a nurse visit by 1.5 (representing nurse time, plus other, i.e., equipment and analysis of results).
#Source: British National Formulary 55 [25], mean dosage 247 mg daily.
MI, myocardial infarction; GP, general practitioner; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

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 3), 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.

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, the Scottish Medicines Consortium, and the Treasury [17,18]. Discount rates were varied in the sensitivity analysis.

One-way sensitivity analyses were carried out 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

Incremental Analysis

Table 5 shows the incremental results. Over a period of 10 years, the valsartan cohort experienced 431 cardiovascular deaths per 1000 patients compared with 578 in the placebo group. The valsartan group experienced 178 nonfatal MIs, 314 cases of heart failure, and 48 strokes over 10 years compared with 215, 409 and 43, respectively, in the placebo group.

Table 5 Incremental results

	Valsartan	Placebo	Incremental
Cost	£8878	£6198	£2680
QALYs	5.021	4.519	0.502
LYs	5.803	5.230	0.574
Incremental cost per QALY			£5338
Incremental cost per LY			£4672

QALY, quality-adjusted life-year; LY, life-year.

In the base case analysis, the valsartan cohort cost an average of £8878 per patient over the 10-year period. In comparison, the placebo cohort cost an average of £6198 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 £2680 per patient. Patients in the valsartan group experienced a total of 5.021 QALYs per patient, compared with 4.519 QALYs in the placebo group. Therefore, 0.502 additional QALYs were gained over the 10 years modeled.

The incremental cost per QALY gained for treatment with valsartan was, therefore, £5338. When the analysis was undertaken using life-years rather than QALYs, the cost per life-year gained was £4672.

One-Way Sensitivity Analysis

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

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 £4726. 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 incremental cost-effective ratio (ICER) increased to £6624. 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 poststroke and postheart failure, and changes in the likelihood of patients discontinuing valsartan.

Probabilistic Sensitivity Analysis

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 1 and 4). The outputs from the PSA show relatively little variation in the incremental costs and outcomes (see Fig. 2). As such, the cost-effectiveness acceptability curve (Fig. 3) shows that there is a high degree of confidence associated with valsartan being a cost-effective intervention.

Discussion

The cost-effectiveness estimate of valsartan after an MI in patients with evidence of left ventricular systolic dysfunction, heart failure, or both, who are unsuitable for ACE inhibitors compared to placebo with a 10-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. Several studies, however, have assessed the cost-effectiveness of ACE inhibitors, including Tsevat et al., who showed that the cost-effectiveness of captopril (compared with placebo) after MI ranged between US$3600 and US$60,800 per QALY (US dollar, 1991 prices), depending on the age of the patient and the persistence of treatment benefits [19]. Martinez and Ball estimated that the cost-effectiveness of ramipril (compared with placebo) was around £300 per life-year gained (1993 prices) [20].

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 (£1317)	£659	5,459	£1,976	5,217
Nonfatal MI (£1177)	£588	5,357	£1,765	5,319
Stroke (£2275)	£1,138	5,321	£3,413	5,355
Heart failure (£1536)	£768	5,419	£2,303	5,256
Other death (£376)	£188	5,335	£564	5,341
Post-MI follow up (£844)	£422	4,793	£1,266	5,882
Post-stroke follow up (£1935)	£967	5,269	£2,902	5,407
Postheart failure follow up (£1076)	£537	5,428	£1,614	5,248
Cost of valsartan (£109 per cycle)	£54	2,990	£163	7,685
QALY				
No complications (and post-MI) (0.88)	0.70	6,624	1	4,726
Post nonfatal stroke (0.68)	0.54	5,394	0.82	5,283
Postheart failure (0.84)	0.67	5,167	1	5,504
Event rates* (First 3 months, later 3 months)				
Valsartan				
Cardiovascular death (6.00%, 1.58%)	4.8%, 1.26%	3,867	7.2%, 1.9%	10,426
Nonfatal MI (0.73%, 0.73%)	0.37%, 0.37%	5,354	1.48%, 1.48%	5,305
Heart failure (1.3%, 1.28%)	0.59%, 0.59%	5,448	2.60%, 2.60%	5,187
Nonfatal stroke (0.20%, 0.20%)	0.10%, 0.10%	5,248	0.40%, 0.40%	5,528
Discontinue due to adverse events (2.90 %, 0.41%)	1.45%, 0.20%	5,309	5.80%, 0.82%	5,397
Other				
Discount rate† (3.5%)	0%	5,127	6%	5,494

*Both first 3-month and subsequent 3-month periods were increased/decreased by 20%.
†Both costs and benefits were discounted at the same rates.
ICER, incrementl cost-effective ratio; MI, myocardial infarction.

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 10-year period can be estimated from the model. In the placebo group of the model, the survival rate for patients after 10 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 with 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 24 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, on the one hand, 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

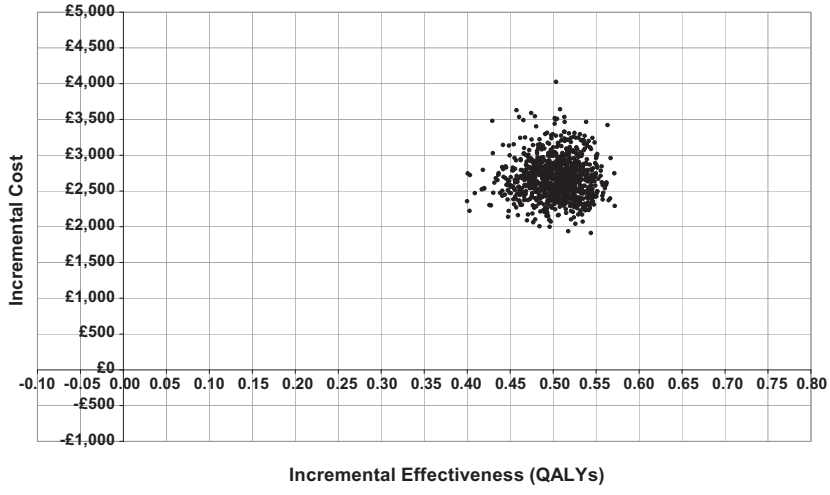

Figure 2 Cost-effectiveness scatter plot. QALYs, quality-adjusted life-year.

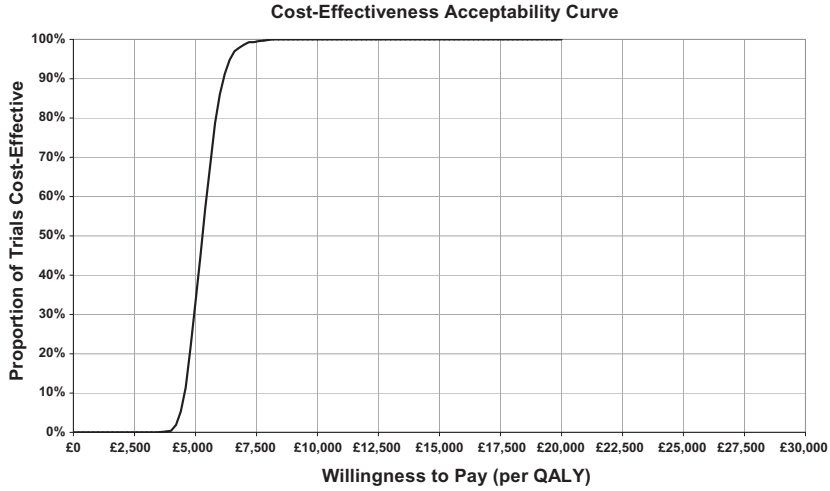

Figure 3 Cost-effectiveness acceptability curve. QALY, quality-adjusted life-year.

would experience similar benefits of valsartan because patients who are suitable for ACE inhibitors. Expert opinion was used for some model inputs where published data were not available. Nevertheless, such use was based on alternate 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. Nevertheless, 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 because patients would switch to a treatment equivalent to that of the comparator group.

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

Conclusions

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 after MI.

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

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