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Potential economic consequences of a cardioprotective agent for patients with myocardial infarction: modelling study

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ABSTRACT

Objective: To investigate the cost-effectiveness of a hypothetical cardioprotective agent used to reduce infarct size in patients undergoing percutaneous coronary intervention (PCI) after anterior ST-elevation myocardial infarction.

Methods: *Design*: A cost-utility analysis using a Markov model. *Setting*: The National Health Service in the UK. *Patients*: Patients undergoing PCI after anterior ST-elevation myocardial infarction. *Interventions*: A cardioprotective agent given at the time of reperfusion compared to no cardioprotection. We assumed the cardioprotective agent (given at the time of reperfusion) would reduce the risk and severity of heart failure (HF) after PCI and the risk of mortality after PCI (with a relative risk ranging from 0.6 to 1). The costs of the cardioprotective agent were assumed to be in the range £1000–4000. *Main outcome measures*: The incremental costs per quality-adjusted life-year (QALY) gained, using 95% CIs from 1000 simulations.

Results: Incremental costs ranged from £933 to £3820 and incremental QALYs from 0.04 to 0.38. The incremental cost-effectiveness ratio (ICER) ranged from £3311 to £63 480 per QALY gained. The results were highly dependent on the costs of a cardioprotective agent, patient age, and the relative risk of HF after PCI. The ICER was below the willingness-to-pay threshold of £20 000 per QALY gained in 71% of the simulations.

Conclusions: A cardioprotective agent that can reduce the risk of HF and mortality after PCI has a high chance of being cost-effective. This chance depends on the price of the agent, the age of the patient and the relative risk of HF after PCI.

Strengths and limitations of this study

- A strength of this study is that a model is presented that can be used for any potential cardioprotective agent to study the economic consequences of implementing this agent in clinical practice. If the effect of the new drug on the incidence of heart failure after PCI is known, this model can be updated to present a more precise estimate of the cost-effectiveness of this drug.
- The main limitation of this study is that it is based on a hypothetical drug. There are currently not enough data available on the long-term effectiveness of any of the potential cardioprotective agents.
- We also assumed that the cardioprotective agent would only reduce the risk and severity of heart failure and not the risk of other clinical major adverse cardiac events, such as recurrent infarction. In reality, a cardioprotective agent might have an effect on all such events. However, by only taking into account heart failure risk we present a conservative estimate of the cost-effectiveness. A cardioprotective agent that will also decrease the risk of other major adverse cardiac events is expected to have a higher chance to be cost-effective.

INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of mortality and morbidity, even with the use of early reperfusion strategies such as percutaneous coronary intervention (PCI). In case of AMI, a coronary artery becomes occluded, causing myocardial ischaemia, which in its turn causes myocardial necrosis. The extent of this necrosis, the infarct size, is a major determinant of mortality and morbidity after AMI. After AMI blood flow in the ischaemic myocardium should therefore be restored as soon as possible to minimise infarct size and associated complications. PCI is frequently used to accomplish this but, may itself cause injury to the myocardium as a consequence of the restoration in blood flow with generation of oxidative stress. The efficacy of reperfusion therapy is often assessed by measuring the infarct size using serum markers or MRI. Cardioprotection could be used at the time of reperfusion to reduce reperfusion injury and further decrease myocardial necrosis. Cardioprotection can be defined as any strategy to preserve the heart by reducing or even preventing myocardial damage.[1] Many cardioprotective strategies
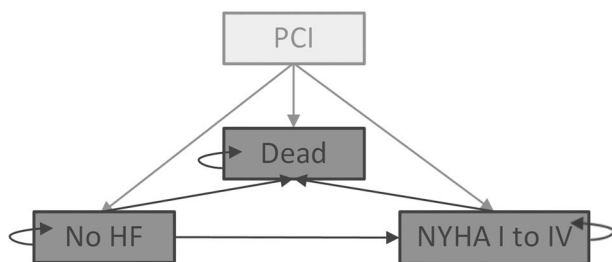
have been developed and tested to reduce reperfusion injury and decrease infarct size.[2–4] These include post-conditioning, remote ischaemic conditioning, intravenous cooling and various pharmacological agents. None of these strategies has yet translated into clinical practice; some did not have the desired effect in clinical trials while others are still in development.[2–4]

The longer term consequences of AMI are not only caused by the direct structural damage inflicted by the infarction, but also by secondary changes in the size and shape of the myocardium (ventricular remodelling). This can lead to ventricular dysfunction with subsequent heart failure (HF), long-term morbidity and a shortened lifespan.[5] [6] By reducing infarct size, cardioprotective agents potentially decrease the incidence and severity of HF after AMI, thereby reducing long-term morbidity which might carry significant economic consequences. Such consequences have not yet been studied. The aim of this study is to investigate the cost-effectiveness of a hypothetical cardioprotective agent used to reduce infarct size in patients undergoing PCI after anterior ST-elevation myocardial infarction (STEMI).

METHODS
Model structure
A Markov model was developed to assess the potential clinical effect and the economic consequences of a cardioprotective agent. It is expected that a reduced infarct size will affect the risk and severity of HF after STEMI. We conservatively assumed that the cardioprotective agent would only reduce the risk and severity of HF and not the risk of other clinical major adverse cardiac events, such as recurrent infarction. Figure 1 depicts the different health states in the Markov model. After PCI a patient could stay alive without HF, develop HF (in any of the four New York Heart Association (NYHA) classes) or die. Other than death, which is an absorbing state, patients either stay in their health state or move to another state in monthly cycles. In the model, patients are unable to recover from having HF, but could move up and down between the different NYHA classes or stay without symptoms (NYHA class 1). Patients who did not have HF directly after PCI may develop HF later. Transitions in any cycle were dependent on time since the start of the model, but not on what happened prior to that cycle (past health states or how long they have been in a particular state). The model was run over a lifetime horizon.

Clinical input
Natural disease history
A literature search was performed to collect relevant data to populate the model. In our base case, patients were 65 years old when having PCI. Clinical outcome after PCI varies among different patient groups. Mortality after PCI has been reported between 3.4%[7] to 7.8%,[8] and the incidence of HF from 5%[9] to almost 30%.[10] [11] We assumed that mortality after PCI would be 3.4% and the incidence of HF 10%. Late onset HF would occur in 5% of patients in the first month after PCI, and a further 0.5% until 2 years after PCI.[9] [11] Clinical input parameters are shown in table 1. Transition probabilities between the different NYHA classes were derived from a randomised trial[12] as in previous cost-effectiveness studies of HF treatment[13] [14] (table 2). Age-specific long-term mortality data of myocardial infarction patients were used to determine the mortality of patients in the 'No HF' or 'NYHA class I' state.[15] This was done by applying monthly transition probabilities for mortality to all survivors of the previous month. An excess mortality risk was applied to patients in the NYHA class II to IV states (0.26–0.72% if not hospitalised, 1.09–5.33% if hospitalised, see table 1). These data, as well as the probability of hospitalisation in the different NYHA classes, were derived from a cost-effectiveness study on the treatment of HF.[13]

Efficacy of hypothetical cardioprotective agent
As the analysis is based on a hypothetical cardioprotective agent, no data on effectiveness were currently available for use in this model. We assumed that the drug would affect the incidence of HF and mortality directly after PCI, as well as the incidence of new HF or worsening of existing HF in the 6 months following PCI. In previous studies on the effectiveness of cardioprotective strategies, varying results were found. In a study on the efficacy of adenosine in AMI it was found that 1 month mortality was reduced from 9.2% to 5.2% (p=0.014) and 6-month mortality was reduced from 11.2% to 7.3% in patients receiving early reperfusion.[21] A small reduction in in-hospital HF was seen, although this was not statistically significant (3.2% vs 4.0%, p=0.59). A larger reduction in HF was seen for ischaemic postconditioning in patients treated with PCI (27% vs 46%, p=0.048).[22] In the current study we therefore assumed a relative risk of these events in the intervention group in the range of 60–100% (point estimate 80%).

Figure 1 Health states in the Markov model. After PCI, patients could move to any of the health states (light grey arrows). In subsequent cycles, patients could stay in the health state or move to another health state (dark grey arrows). In the model, patients are unable to recover from having HF, but could move up and down between the different NYHA classes or stay without symptoms (NYHA class 1). Patients who did not have HF directly after PCI may develop HF later. HF, heart failure; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Table 1 Input parameters

Parameter	Base case value	Lower limit	Upper limit	Distribution	Source
Age (years)	65	55.00*	75.00*	Normal (μ:65, SD: 5)	Assumption
Probabilities without intervention					
Outcome after PCI					
Heart failure	10.00%	7.38%†	12.62%†	Dirichlet‡ (50, 17, 434)	[9–11]
Mortality	3.39%	1.81%†	4.98%†		[7]
Percentage of heart failure patients in each NYHA class					
NYHA I	23.00%	16.17%†	29.83%†	Dirichlet‡ (34, 71, 32, 7)	[9]
NYHA II	50.00%	41.89%†	58.11%†		[9]
NYHA III	22.00%	15.28%†	28.72%†		[9]
NYHA IV	5.00%	1.46%†	8.54%†		[9]
New onset HF, monthly probability					
First month	5.00%	0.00%*	10.00%*	β (α: 3.8, β: 71.3)	[9, 11]
Month 2–24	0.02%	0.00%*	0.04%*	β (α: 4.3, β: 20 824)	[9]
After 24 months	0.00%				Assumption
RR with cardioprotection compared to no cardioprotection					
Heart failure after PCI	80%	60.00%*	100.00%*	Uniform (0.6–1)	Assumption
Mortality after PCI	80%	60.00%*	100.00%*	Uniform (0.6–1)	Assumption
Develop new HF, first 6 months	80%	60.00%*	100.00%*	Uniform (0.6–1)	Assumption
Worsening HF, first 6 months	80%	60.00%*	100.00%*	Uniform (0.6–1)	Assumption
Probability of hospitalisation (per month)					
NYHA I	1.52%	0.03%*	3.01%*	β (α: 3.9, β: 254.4)	[13]
NYHA II	2.40%	0.05%*	4.75%*	β (α: 3.9, β: 157.9)	[13]
NYHA III	2.40%	0.05%*	4.75%*	β (α: 3.9, β: 157.9)	[13]
NYHA IV	15.40%	0.31%*	30.49%*	β (α: 3.2, β: 17.8)	[13]
Excess mortality (per month)					
When hospitalised class II	1.09%	0.08%†	2.23%†	β (α: 4.0, β: 396)	[13]
When not hospitalised class II	0.26%	0.00%†	0.50%†	β (α: 4.4, β: 1690)	[13]
When hospitalised class III	1.79%	0.69%†	3.04%†	β (α: 9.0, β: 499)	[13]
When not hospitalised class III	0.67%	0.22%†	1.15%†	β (α: 8.3, β: 1218)	[13]
When hospitalised class IV	5.33%	2.66%†	9.25%†	β (α: 9.9, β: 175)	[13]
When not hospitalised class IV	0.72%	0.00%†	1.88%†	β (α: 2.3, β: 319)	[13]
Utilities (quality of life)					
After PCI (no heart failure)	0.86	0.85†	0.87†	β (α: 2426, β: 395)	[16]
NYHA I	0.82	0.78†	0.85†	β (α: 396, β: 90)	[13]
NYHA II	0.72	0.69†	0.75†	β (α: 662, β: 257)	[13]
NYHA III	0.59	0.55†	0.63†	β (α: 360, β: 250)	[13]
NYHA IV	0.51	0.41†	0.60†	β (α: 52, β: 50)	[13]
Hospitalisation (decrement)	−0.10	0.00*	−0.20*	β (α: 3.5, β: 31.5)	[13]
Costs per event					
Myocardial infarction and PCI	£4158	£83*	£8233*	γ (α: 4, β: 1223)	[17]
Cardioprotective agent	£2500	£1000*	£4000*	Uniform (1000–4000)	Assumption
Hospitalisation	£1535	£96*	£2974*	γ (α: 4, β: 499)	[17]
Costs per month					
Pharmaceutical therapy NYHA I	£5	£3*	£12*	γ (α: 4, β: 0.50)	[18, 19]
Pharmaceutical therapy NYHA II	£5	£3*	£12*	γ (α: 4, β: 0.50)	[18, 19]
Pharmaceutical therapy NYHA III	£11	£7*	£18*	γ (α: 4, β: 1.00)	[18, 19]
Pharmaceutical therapy NYHA IV	£15	£9*	£22*	γ (α: 4, β: 1.25)	[18, 19]

*Based on assumption.
†Based on 95% CI.
‡Using the methods described by Briggs et al.[20]
HF, heart failure; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Health utility

The health utility after PCI, without HF, was 0.86 in our model based on results from the EuroQol Questionnaire as in previous studies.[16 23] Patients with HF had a lower quality of life, depending on the severity of the disease, varying from 0.82 in NYHA class I to 0.51 in NYHA class IV.[13 14] When a patient was hospitalised, a temporary decrement of 0.10 was applied in the month following hospitalisation.[13 14]

Costs

The perspective of this cost-effectiveness analysis was the cost to the National Health Service (NHS). Costs of AMI, PCI and HF events were derived from the NHS

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Table 2 Monthly transition probabilities among NYHA class[12–14]

From↓ to→	NYHA I (%)	NYHA II (%)	NYHA III (%)	NYHA IV (%)
NYHA I	97.70	1.90	0.40	0.00
NYHA II	0.80	98.10	1.00	0.10
NYHA III	0.00	3.40	96.00	0.60
NYHA IV	0.00	0.00	5.50	94.50

Values were varied in the probabilistic sensitivity analysis using Dirichlet distributions.[20]
NYHA, New York Heart Association.

reference cost schedule 2012/2013.[17] The monthly costs of the pharmaceutical treatment of HF were calculated using information on drug use in the different NYHA classes from a previous cost-effectiveness analysis[19] and applying 2014 National formulary unit prices.[18] We assumed that the drug would be administered at the time of reperfusion and would not affect the length of stay in the hospital or the need for diagnostic tests. For the cost of a new cardioprotective agent we assumed a one-off, one-time treatment of £2500 and because this is a hypothetical agent, we varied this over a wide range (£1000–£4000). Future costs and effects were discounted at an annual rate of 3.5%.

Analysis

The main outcome of our analysis was the incremental costs per quality-adjusted life-year (QALY) gained which is the recommended cost-effectiveness measure for economic evaluations in England.[24] Because there are currently no data available on the effect and costs of a cardioprotective agent, these parameters were varied over a wide range. To assess the uncertainty of the model we undertook several sensitivity analyses. First, all parameters, such as the cost of a cardioprotective agent, the cost of hospitalisation, the relative risk of HF with a cardioprotective agent, the relative risk of mortality after PCI with a cardioprotective agent, and the incidence of HF after PCI were varied in a one-way sensitivity analysis. Upper and lower limits were based on 95% CIs if available, otherwise assumptions about the range were made. For some parameters, such as the '% of patients with HF in each NYHA class', when one value was changed in the sensitivity analyses, the other values were changed simultaneously so that the sum would always be 100% (adding or subtracting the change in the parameter that was tested from the largest category). Second, the price and effect of a cardioprotective agent were varied simultaneously in a two-way sensitivity analysis to identify combinations of these values at which the ICER would be below £20 000 per QALY gained. Lastly, a probabilistic sensitivity analysis was carried out, drawing random samples from the probability distributions of all parameters in 1000 simulations, using the distributions in table 1. The proportion of times the ICER was less than the cost-effectiveness threshold was calculated for

different values of the cost-effectiveness threshold, ranging from £0 to £50 000, and presented graphically using cost-effectiveness acceptability curves.
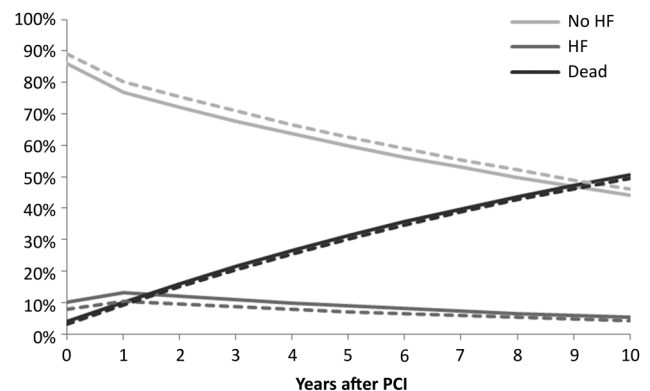
RESULTS

Base case

As shown in figure 2, the percentage patients without HF decreased overtime, while the percentage of patients with HF initially increased, but decreased after the first year as more patients died. When a relative risk of 80% was used for events in users of a cardioprotective agent, the number of patients without HF was approximately 3% higher when a cardioprotective agent was used and the number of patients with HF approximately 2% lower. The percentage of patients who died was approximately 1% lower with a cardioprotective agent.

From the 1000 simulations, a 95% confidence range could be calculated. The costs without use of a cardioprotective agent ranged from £1793 to £10 963 (mean £5163) and QALYs ranged from 3.95 to 12.89 (mean 8.34). Patients lived on average 9.60 (SD: 2.39) years after STEMI. With the use of a cardioprotective agent, costs ranged from £3702 to £13 190 (mean £7498) and QALYs from 4.01 to 13.12 (mean 8.52). Patients were expected to live on average 9.77 (SD: 2.45) years after STEMI. Incremental costs were £933 to £3820 (mean £2334) and incremental QALYs 0.04 to 0.38 (mean 0.18). The ICER ranged from £3311 to 63 480 per QALY gained (mean £13 014). The results are summarised in table 3.

Sensitivity analysis

As expected, the costs of a cardioprotective agent and the relative risk of HF after PCI with a cardioprotective agent had a large influence on the cost-effectiveness results in our one-way sensitivity analysis. If the costs of a cardioprotective agent would be £1000, the ICER would be £4878, while if the costs would be £4000 the ICER would be £22 004 per QALY gained. Other factors that had a large influence on the ICER were age and relative

Figure 2 Percentage of patients with or without HF or who died. Solid line: no cardioprotection, dashed line: with cardioprotective agent. HF, heart failure; PCI, percutaneous coronary intervention.

Table 3 Results (95% CIs) from the 1000 simulations

	Costs (£)	QALYs	ICER (£/QALY)
No cardioprotection	£5163 (1793 to 10 963)	8.34 (3.95 to 12.89)	
Cardioprotective agent	£7498 (3702 to 13 190)	8.52 (4.01 to 13.12)	
Increment	£2334 (933 to 3820)	0.18 (0.04 to 0.38)	£13 014 (3311 to 63 480)

QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

risk of mortality after PCI with a cardioprotective agent. The ICER would exceed a threshold of £20 000 in patients older than 70 and £30 000 in patients older than 74. The effect of uncertainty around several key parameters on the ICER is shown in the tornado diagram in figure 3.

When the price and effect of a cardioprotective agent were varied simultaneously we found that if the relative risk of the cardioprotective agent would be 0.6 (preventing 40% of HF cases and mortality after PCI and also preventing 40% of new HF cases or worsening of HF in the following 6 months) the price of the cardioprotective agent could be as high as £6660 and still be below the £20 000 threshold. If the relative risk would only be 0.95, however, the price should be no higher than £826. The results of this two-way analysis are shown in figure 4. The incremental cost-effectiveness ratios at various relative risk and cost values are shown in online supplementary table S1.

In the probabilistic sensitivity analysis, the ICER was below £20 000 per QALY gained in 71% of the simulations. At a willingness-to-pay of £30 000 per QALY gained, this probability would be 87%. The probability that a cardioprotective agent would be cost-effective at different thresholds is shown in figure 5.

DISCUSSION
In this study we have investigated the potential economic consequences of a hypothetical cardioprotective agent.

The results of this study indicate that if a cardioprotective agent could be successfully developed for patients with STEMI to decrease the risk of HF after PCI, it has a high chance of being cost-effective. Currently there are no such cardioprotective agents available, but it is expected that this will change in the near future. In a randomised trial of the cardioprotective effects of hypothermia using cold saline and endovascular cooling the incidence of HF was significantly lower in the hypothermia group than in the control group (3% vs 14%).[25] In this trial, no overall effect was shown on infarct size, however, the infarct size was significantly smaller in the subset of patients with anterior STEMI. In a small randomised trial cyclosporine reduced infarct size,[26] but this effect could not be replicated in a more recent larger trial.[27] The antiplatelet drug abciximab reduced 30-day infarct size when administered intravenously, but no significant effect on HF was demonstrated.[28] Intracoronary administration of this drug did not result in a lower risk of mortality or recurrent infarction, but did result in a lower risk of new HF (2.4% vs 4.1%) compared to intravenous administration.[29] The antidiabetic drug exenatide could also reduce infarct size, but only in those reperfused early.[30][31] In a recent trial, patients treated with metoprolol before PCI had a smaller infarct size and higher left ventricular ejection fraction.[32] These trials all suggest there are many potential cardioprotective agents that could affect the outcome of myocardial infarction. Several reviews on this topic therefore

Figure 3 Tornado diagram showing the effect of uncertainty around the most influential parameters on the incremental cost-effectiveness ratio. HF, heart failure; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.
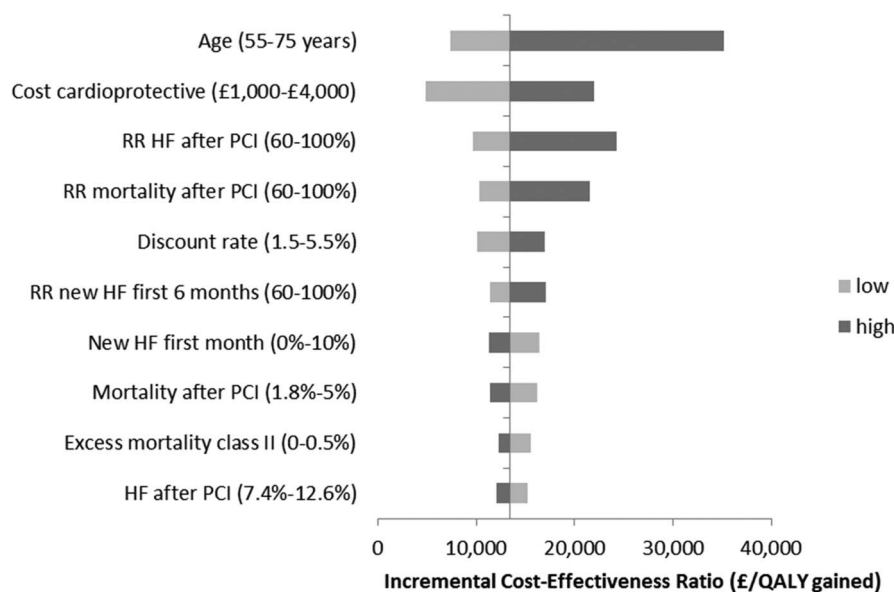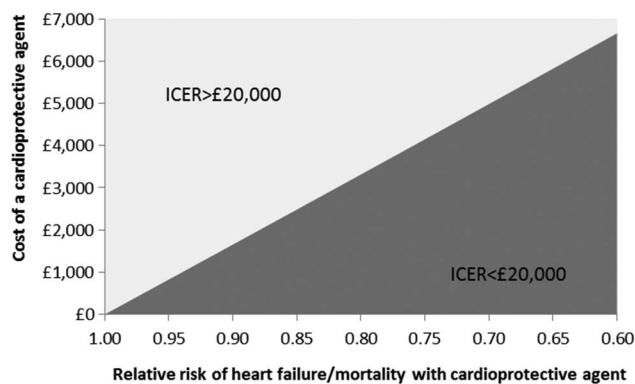
Figure 4 Results of the two-way sensitivity analysis. The ICER would be higher than £20 000 per QALY gained in scenarios represented by the light grey area, while the ICER would be below this threshold in scenarios represented by the dark grey area. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

conclude that it is likely that treatment of reperfusion injury will become available in the near future.[2–4]

The economic burden of HF resulting from AMI has been estimated to be at least £125–181 million to the NHS and a further £27 million for nursing home costs in 2000.[33] The cost-effectiveness of treatment for post-myocardial infarction HF was studied in several countries, such as the USA, Germany, the Netherlands, France and Spain[34] and also in the UK, where aldosterone antagonists were found to be a highly cost-effective strategy for the management of HF.[35] However, no studies have been published up to this date on cardioprotective agents to prevent HF in patients with AMI.

There was considerable uncertainty around many input parameters in the model. This was caused by the lack of specific data about the effectiveness and costs of a cardioprotective agent (due to the hypothetical character of the study) or the small sample size of some studies we used to predict variables in our analysis. We accounted for this uncertainty by varying the parameters over their 95% CIs or other (wide) plausible range in the probabilistic sensitivity analysis. In this sensitivity
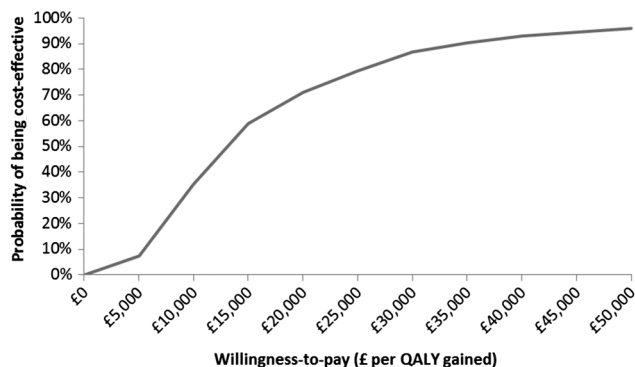
Figure 5 Cost-effectiveness acceptability curve. QALY, quality-adjusted life-year.

analysis we performed 1000 simulations to be able to calculate CIs around our results.

The main limitation of this study is that it is based on a hypothetical drug. There is currently not enough data available on the long-term effectiveness of any of the potential cardioprotective agents. We also assumed that the cardioprotective agent would only reduce the risk and severity of HF and not the risk of other clinical major adverse cardiac events, such as recurrent infarction. In reality, a cardioprotective agent might have an effect on all such events. However, by only taking into account HF risk we present a conservative estimate of the cost-effectiveness. A cardioprotective agent that will also decrease the risk of other major adverse cardiac events is expected to have a higher chance to be cost-effective. Future studies should provide more data on the long-term effectiveness of new agents, looking at on-target as well as off-target effects and ideally also at the quality of life. A strength of this study is that a model is presented that can be used for any of the potential cardioprotective agents to study the economic consequences of implementing this agent in clinical practice. If the effect of the new drug on the incidence of HF after PCI is known, this model can be updated to present a more precise estimate of the cost-effectiveness of this drug. For this future research an update of the estimates of relative risks for mortality and HF after PCI is required and if applicable, other benefits of the treatment can be added to the model.

The chance that a new cardioprotective agent will be cost-effective mainly depends on the price of the agent, the age of the patient and the relative risk of HF after PCI. To be cost-effective a higher price for the drug requires a greater effect on HF incidence or mortality. At a price of £2500 and with a 20% reduction in HF incidence and mortality after PCI, it is likely that the cardioprotective agent would be cost-effective.

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Table S1. Cost-effectiveness results at different values for relative risk of heart failure and costs of the cardioprotective agent

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RR: 95%, costs: £1000	£967	0.04	£24,387
RR: 95%, costs: £2000	£1,967	0.04	£49,602
RR: 95%, costs: £3000	£2,967	0.04	£74,818
RR: 95%, costs: £4000	£3,967	0.04	£100,033
RR: 85%, costs: £1000	£901	0.12	£7,556
RR: 85%, costs: £2000	£1,901	0.12	£15,942
RR: 85%, costs: £3000	£2,901	0.12	£24,328
RR: 85%, costs: £4000	£3,901	0.12	£32,714
RR: 75%, costs: £1000	£834	0.20	£4,189
RR: 75%, costs: £2000	£1,834	0.20	£9,209
RR: 75%, costs: £3000	£2,834	0.20	£14,229
RR: 75%, costs: £4000	£3,834	0.20	£19,250
RR: 65%, costs: £1000	£767	0.28	£2,745
RR: 65%, costs: £2000	£1,767	0.28	£6,323
RR: 65%, costs: £3000	£2,767	0.28	£9,901
RR: 65%, costs: £4000	£3,767	0.28	£13,479