CORONARY ARTERY DISEASE

Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study

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A supplementary technical appendix is available on the Heart website—<http://heart.bmj.com/supplemental>

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Background: The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial has recently reported.

Objective: To assess the cost effectiveness of perindopril in stable coronary heart disease in the UK.

Methods: Clinical and resource use data were taken from the EUROPA trial. Costs included drugs and hospitalisations. Health-related quality of life values were taken from published sources. A cost-effectiveness analysis is presented as a function of the risk of a primary event (non-fatal myocardial infarction, cardiac arrest or cardiovascular death) in order to identify people for whom treatment offers greatest value for money.

Results: The median incremental cost of perindopril for each quality-adjusted life year (QALY) gained across the heterogeneous population of EUROPA was estimated as £9700 (interquartile range £6400–£14 200). Overall, 88% of the EUROPA population had an estimated cost per QALY below £20 000 and 97% below £30 000. For a threshold value of cost effectiveness of £30 000 per QALY gained, treatment of people representing the 25th, 50th (median) and 75th centiles of the cost effectiveness distribution for perindopril has a probability of 0.999, 0.99 and 0.93 of being cost effective, respectively. Cost effectiveness was strongly related to higher risk of a primary event under standard care.

Conclusions: Whether the use of perindopril can be considered cost effective depends on the threshold value of cost effectiveness of healthcare systems. For the large majority of patients included in EUROPA, the incremental cost per QALY gained was lower than the apparent threshold used by the National Institute for Health and Clinical Excellence in the UK.

Despite improvement in the prognosis of patients with cardiovascular disease over the past few decades with the use of aspirin, statins and β blockers, such patients remain at high risk of further complications and premature mortality. Angiotensin-converting-enzyme (ACE) inhibitors have previously been shown to improve survival and to reduce the rate of myocardial infarction (MI) and the need for revascularisation in patients with heart failure and left ventricular dysfunction.^{1,2} The Heart Outcomes Prevention Evaluation (HOPE) study indicated the benefits of ACE inhibition in stable patients at high risk of cardiovascular events.³ In addition to reducing blood pressure, there is evidence that ACE inhibitors may have anti-atherosclerotic effects,^{4–6} which suggests that ACE inhibition may be of value in all patients with established coronary heart disease.

The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) study evaluated this hypothesis directly.⁷ The trial randomised 12 218 patients with stable coronary heart disease to the ACE inhibitor perindopril 8 mg once daily or to matching placebo. Over a mean follow-up of 4.2 years, the trial showed that the use of perindopril resulted in a 20% relative risk reduction in the primary end point of cardiovascular death, MI or cardiac arrest (from an average risk of 9.9% in the placebo arm to 8.0% in the perindopril arm). These results suggest that use of perindopril should be considered, in addition to other preventive drugs, in all patients with coronary heart disease. Indeed, both the European Medicines Evaluation Agency in

Europe and the Federal Drug Agency in the US have licensed the use of perindopril for patients with existing coronary disease on the basis of the results of the EUROPA study. Nevertheless, the appropriateness of the decision to use perindopril for its licensed indication in a resource-constrained health system will depend upon its cost effectiveness—that is, on whether it improves patients' quality-adjusted life expectancy at an acceptable cost. This paper reports on a cost-effectiveness analysis of this policy based on data collected within the EUROPA trial.

METHODS

The analysis assesses the cost effectiveness of the clinical policy examined in the EUROPA trial—that is, to provide perindopril 8 mg once daily to patients with stable coronary heart disease, without apparent heart failure or hypertension. In the base-case analysis, treatment is assumed to last for 5 years or until death as this was the treatment period in EUROPA. The perspective of the UK National Health Service is adopted and health outcomes are assessed as quality-adjusted life years (QALYs). The time horizon of the analysis is 50 years and costs and future QALYs were discounted at an annual rate of 3.5%.⁸

Abbreviations: EUROPA, European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE, Heart Outcomes Prevention Evaluation; HRQL, health-related quality of life; QALY, quality-adjusted life year; PEACE, Prevention of Events with Angiotensin Converting Enzyme Inhibition

Table 1 Estimated risk equations for the risk of a first primary event (equation 1), the odds of that event being fatal (equation 2) and the risk of a further primary event in the first year after a first non-fatal event (equation 3)

Explanatory baseline characteristics	Equation 1: Risk of first primary event (1069 events)*			Equation 2: Odds that first event is fatal (400 events)			Equation 3: Risk of subsequent event in first year after initial non-fatal event		
	Hazard ratio	Lower 95% limit	Upper 95% limit	Odds ratio	Lower 95% limit	Upper 95% limit	Hazard ratio	Lower 95% limit	Upper 95% limit
Use of perindopril	0.81	0.71	0.91						
Age				1.04	1.03	1.05			
Years older than age 65	1.06	1.04	1.08						
Male	1.54	1.28	1.87						
Smoker	1.49	1.27	1.74						
Previous MI	1.44	1.26	1.66	1.60	1.19	2.14			
Previous revascularisation	0.88	0.77	0.99						
Existing vascular disease†	1.69	1.44	1.98						
Diabetes mellitus	1.49	1.28	1.74						
Family history of coronary artery disease	1.21	1.05	1.38						
Symptomatic angina‡ or history of heart failure	1.32	1.16	1.51				1.85	1.29	2.64
Systolic blood pressure	1.00	1.00	1.01						
Units creatinine clearance below 80 ml/min	1.01	1.00	1.02						
BMI > 30 (obese)	1.41	1.22	1.63						
Total cholesterol	1.13	1.07	1.20	1.21	1.08	1.35			
Using nitrates at baseline	1.42	1.25	1.63						
Using calcium channel blockers at baseline	1.20	1.06	1.36						
Using lipid-lowering treatment at baseline	0.86	0.75	0.97						
Constant term (on the log scale)	-12.27	-12.97	-11.57	-4.37	-5.54	-3.20	-6.46	-7.25	-5.67
Ancillary parameter							0.70	0.59	0.82

BMI, body mass index; MI, myocardial infarction.

*Primary trial end point of cardiovascular mortality, MI or cardiac arrest.

†Any of stroke, transient ischaemic attack or peripheral vascular disease.

‡Canadian Cardiovascular Society Angina Scale²¹ levels 2–4, higher level relates to worse symptoms.

To project the analysis beyond the 4.2-year mean follow-up of EUROPA, a Markov state transition model⁹ was developed, based on the occurrence of the primary event (non-fatal MI, cardiac arrest or cardiovascular death) in the trial. Five health states were defined as “absence of primary event in trial”, “cardiovascular death”, “non-fatal primary event in current year”, “history of non-fatal event” and “non-cardiovascular death”. Transitions between the first four of these health states were estimated from risk equations based on the EUROPA data. With the addition of data from UK life tables on mortality rates for non-cardiovascular reasons, the risk equations facilitate simulation of the fatal and non-fatal events that a cohort of patients is expected to experience with and without perindopril.

The model assumes that all patients in the treatment arm take perindopril at a cost of £10.95 per 30 tablet pack (or 37p a day).¹⁰ This cost reflects a price reduction in the cost of perindopril that came into effect on 11 January 2005. All other costs in the EUROPA study are estimated for the period 2003–4. Costs of other drug use recorded in EUROPA were estimated using the UK Department of Health Prescription Cost Analysis database.¹¹ Hospitalisation costs were taken from UK Trust Financial Returns, which report costs per day by specialty.¹² Costs for the model states are based on the experience of events and were estimated using regression methods from these observed drug and hospitalisation costs in the EUROPA study.

Because no health-related quality of life (HRQL) data were collected in EUROPA, the mean age- and sex-specific HRQL scores were estimated from the second Welsh Health Survey,¹³ which collected SF-36 data¹⁴ from a general population survey, and additionally asked subjects whether they had a history of angina or heart attack. SF-36 scores were used to calculate SF-6D¹⁵ utility scores using a previously published algorithm.¹⁶ All subjects in EUROPA were assigned an age/sex-dependent utility score further reduced by the estimated disutility of having angina. For those experiencing a primary event, a further utility decrement associated with experiencing a heart attack was applied.

There is considerable variation in the characteristics of patients who are likely to be considered as having stable coronary artery disease, and the absolute benefit of the use of perindopril is likely to vary according to these characteristics. This variability (or heterogeneity) does not result from perindopril being more effective in some subgroups than others: EUROPA showed that the relative risk reduction from its use was similar across different types of patient.^{7–17} Rather, heterogeneity in absolute benefit is the result of differences between groups in baseline primary event rates (ie, event rates in the absence of perindopril). The cost effectiveness of perindopril is driven by its absolute benefit, so it is estimated dependent on a patient's clinical and demographic features. This is achieved by estimating the variability in baseline primary event rates based on the risk equations, and applying a constant relative risk reduction from the use of perindopril. Given the large potential heterogeneity between patients, the predicted cost effectiveness of perindopril was estimated for each individual patient in the trial and illustrated using five patients chosen from this distribution. One of these patients has the median cost effectiveness of the population, two represent the interquartile range, and the final two represent the 2.5th and 97.5th centiles of cost effectiveness.

Estimates of cost effectiveness for each patient subgroup are subject to uncertainty. To reflect this, a probabilistic sensitivity analysis is undertaken whereby inputs into the analysis are introduced as probability distributions which reflect the precision with which they are estimated, and a Monte Carlo simulation is used to translate the precision in each input variable into a measure of uncertainty in overall cost effectiveness.¹⁸ This is presented for the five indicative risk levels using a 95% uncertainty interval, and using cost-effectiveness “acceptability” which summarises the probability that perindopril is cost effective dependent on how much the health service is willing to pay for an additional QALY.^{19–20} Uncertainty in the assumptions if the analysis is assessed using scenario analyses.

Table 2 Concomitant cardiac drugs and inpatient hospital days taken from the EUROPA trial, together with daily cost

		Mean number of 6-monthly prescriptions per patient	
	Cost/day (£)	Perindopril	Placebo
<i>Concomitant cardiac drugs*</i>			
Platelet inhibitors	0.03	7.634	7.651
Non-study ACE inhibitors	0.47	0.198	0.260
Oral anticoagulants	0.08	0.458	0.450
Angiotensin II RAs	0.70	0.040	0.026
β Blockers	0.07	5.827	5.920
Other vasodilators	0.11	0.411	0.468
Nitrates	0.27	3.780	3.822
Digitalis	0.81	0.149	0.162
Calcium channel blockers	0.43	2.928	3.193
Potassium-sparing diuretics	0.37	0.220	0.277
Lipid-lowering agents	0.79	6.188	6.183
Other diuretic agents	0.05	0.897	1.114
Antiarrhythmic drugs	0.86	0.294	0.295
<i>Inpatient days in hospital by specialty†</i>			
		Mean number of days per patient	
Cardiology	515	2.765	3.082
General surgery	401	0.997	0.953
Cardiac surgery	871	0.868	0.798
Other medicine	225	0.552	0.572
Neurology	379	0.392	0.428
Urology	369	0.329	0.316
Gastroenterology	316	0.215	0.235
Orthopaedics	429	0.264	0.216
Thoracic medicine	259	0.142	0.206

*Daily cost is weighted average across the most commonly prescribed drugs in class.

†Only those specialties with more than 1000 inpatient days in total in the placebo group are reported.

These relate to the duration of treatment and the treatment effect of perindopril subsequent to an initial primary event.

A full technical report of the analysis is available from the *Heart* website (<http://heart.bmj.com/supplemental>).

RESULTS

Risk equations

Table 1 details the fitted risk equations. Equation 1 shows the hazard ratios associated with the risk of a first cardiac event (the trial primary end point of cardiovascular death, MI or cardiac arrest). Of note is the approximately 20% risk reduction associated with being randomised to perindopril (as reported in the main trial report⁷). Other characteristics found to be protective were younger age, being female, previous revascularisation and

cholesterol-lowering treatment. Among characteristics found to increase risk were being a smoker, having had a previous MI and symptomatic angina. Risk equation 2 was a logistic regression estimating the odds of the first cardiac event being fatal. It can be seen that only three characteristics were important enough to enter this equation: being older, having had a previous MI and increased levels of total cholesterol were all found to increase the odds of the event being fatal. Importantly, the use of perindopril was not found to influence the risk of the event being fatal.

Equation 3 considered the risk of a subsequent event in the year after an initial event. Just one characteristic was found to be important in explaining this risk: the presence of angina symptoms (levels 2, 3 or 4 on the Canadian Cardiovascular Society's Angina Scale²¹) increased the risk of a subsequent

Table 3 Results of the cost regression showing costs for the different model states and the impact of covariates

Covariate	Cost (£)	SE	95% CI	
			Lower	Upper
NFE	9775	428	8936	10 613
NFE history	816	117	586	1046
Fatal event	3015	367	2295	3735
NCD	10 285	889	8543	12 026
Age in years	11	2	7	15
Existing vascular disease	325	62	202	447
Diabetes mellitus	209	56	99	320
Symptomatic angina or heart failure	234	41	154	315
Creatinine clearance below 80 ml/min	7	2	2	11
Using nitrates at baseline	226	33	161	292
Using calcium channel blockers at baseline	157	34	90	223
Using lipid-lowering treatment at baseline	100	32	37	163
Treated in UK	-88	39	-165	-12
(Constant)	-17	121	-254	220

NCD, non-cardiovascular death; NFE, non-fatal event.

*Stroke, transient ischaemic attack or peripheral vascular disease.

Table 4 Cost effectiveness of perindopril in five illustrative patients

	Centiles of cost effectiveness				
	2.5th	25th	50th	75th	97.5th
5-Year risk (%)	29	14	8	7	3
Age in years	57	57	58	55	64
Male	1	1	1	1	0
Smoker	1	0	1	0	0
Previous MI	1	1	1	0	0
Previous revascularisation	0	0	1	1	1
Existing vascular disease*	1	0	0	0	0
Diabetes mellitus	0	1	0	1	0
Family history of coronary artery disease	0	0	0	0	0
Symptomatic angina or heart failure	1	1	0	0	0
Systolic blood pressure	150	150	120	110	145
Creatinine clearance below 80 ml/min	105	95	70	98	56
BMI > 30 (obese)	0	0	0	0	0
Total cholesterol	5.22	3.9	6.03	4.6	5
Using nitrates at baseline	1	1	0	1	0
Using calcium channel blockers at baseline	1	0	0	0	0
Using lipid-lowering treatment at baseline	1	1	1	0	0
Incremental cost of perindopril (£)	390	346	478	443	499
Incremental QALYs with perindopril	0.104	0.054	0.049	0.031	0.016
Incremental cost-effectiveness ratio (£)	3729	6 408	9 700	14 163	31 195
Lower 95% limit (£)	2400	3 200	5 500	6 800	17 200
Upper 95% limit (£)	9000	17 000	24 000	40 000	83 000
Probability that cost effective at £30 000/QALY	1.00	1.00	0.99	0.93	0.41
Probability that cost effective at £20 000/QALY	1.00	0.99	0.94	0.75	0.08

BMI, body mass index; MI, myocardial infarction; QALY, quality adjusted life year.

*Stroke, transient ischaemic attack or peripheral vascular disease

event; the ancillary parameter of this analysis indicates a sharply falling hazard of subsequent events over time. Owing to the sparseness of the data, equation 1 is used to estimate the risk of subsequent primary events one or more years after an initial non-fatal event, with the non-fatal event covariate having been updated. This equation also includes a treatment effect of perindopril, so the model effectively assumes that continued treatment will reduce the risk of subsequent, as well as initial, events.

Costs

Table 2 details (per patient) the numbers of 6-monthly prescriptions of concomitant drugs and days of inpatient hospitalisation (by specialty) observed in each randomised group in the EUROPA trial, together with the cost per day of each category of resource use. The most frequently used drugs were platelet inhibitors, β blockers, calcium channel blockers and lipid-lowering agents, but the differences between the randomised groups were small. The most inpatient days in hospital related to the cardiology specialty, for which there were slightly fewer days per patient in the perindopril group. For the other main specialties, days in hospital were similar between the two groups.

The regression analysis on costs (table 3) indicates a "background" annual cost for each surviving patient that depends on age, presence of any existing disease, presence of angina symptoms, creatinine clearance and the use of nitrates, calcium channel blockers or lipid-lowering agents at baseline. In addition to these background costs, the regression model predicts the additional costs associated with the modelled events in the trial. In the year in which a non-fatal primary event occurs, £9775 is added to the background cost. In subsequent years, the addition over the background cost is £816. In the year that a fatal cardiovascular event occurs, the additional cost is estimated as £3015, which contrasts with an additional cost of £10 285 in the year of a non-cardiovascular death. This difference can be explained by the fact that cardiovascular death is often relatively quick compared with other types of death. A dummy variable was included in the

model to represent patients treated in the UK, which suggests that those treated in the UK may incur costs approximately £88 lower than those of patients treated in other European countries.

Cost effectiveness

Overall, the use of perindopril results in added costs to the healthcare system but, because of the reduced risk of cardiovascular events (table 1), increases mean quality-adjusted survival duration. The incremental cost per QALY gained of using perindopril varies according to the patient's characteristics. The median (interquartile range) of the distribution is £9700 (£6400–14 200) per QALY gained.

In table 4, the cost effectiveness of perindopril is considered in more detail for five illustrative patients from the rank ordering of cost effectiveness. The table shows that perindopril is highly cost effective in the patient at greatest risk (29% over 5 years) with a cost per QALY of £3700 (95% interval £2200 to £9400). This is not because its use in this type of patient has a lower additional cost, but because treatment generates a markedly greater gain in QALYs owing to the risk reduction conferred by the use of perindopril in those at greater baseline risk. For the lower-risk patients, the cost per QALY is correspondingly higher because the baseline risks of events in these patients are lower. In addition to the uncertainty intervals, table 4 shows cost-effectiveness acceptability values which summarise, for key threshold values of a QALY, the strength of evidence in favour of the intervention being cost effective.^{19 20} If decision makers are willing to pay, for example, £30 000 per QALY gained, perindopril has a probability of 0.999, 0.99 and 0.93 of being cost effective in people representing the 25th, 50th and 75th centiles of cost effectiveness, respectively. At a threshold of £20 000 per QALY gained, those probabilities fall to 0.99, 0.94 and 0.75, respectively.

Sensitivity analyses

A number of scenarios were run to explore the importance of assumptions employed in the analysis. The first was to assume that treatment with perindopril would be continuous (as opposed to 5 years in the base-case analysis). This alternative

scenario leads to additional cost but also to higher QALYs, and the cost effectiveness of perindopril is similar to that for 5-year treatment. A second scenario explored the assumption that perindopril continues to have a protective effect on those events subsequent to a first event. Removing this assumption had very little impact on the results whether treatment was assumed to last for 5 years or for lifetime. Removing the UK cost adjustment of £88 lower treatment costs and an alternative assumption for quality of life effects based on population norms deflated by a constant proportion to allow for angina also had very little effect on the results. These scenario analyses are presented in full detail in the supplementary technical appendix (available at <http://heart.bmj.com/supplemental>).

DISCUSSION

This cost effectiveness analysis of the use of perindopril in stable coronary heart disease was based largely on clinical and resource use data collected in EUROPA augmented with evidence from routine UK and published sources. The study indicates that the efficacy results seen in EUROPA⁷ are translated into a higher mean quality-adjusted survival duration in patients receiving perindopril. The prevention of cardiac events with perindopril results in some offset to the acquisition cost of the treatment, but it remains the case that healthcare systems will have to identify additional resources to fund this policy. The incremental cost per QALY gained from the use of perindopril provides an indication of whether it is likely to be considered good value. In the UK, guidelines from the National Institute of Health and Clinical Excellence (NICE) and analyses of their past decisions suggest that ratios below £20 000–£30 000 are likely to be considered good value.^{22–24} The results here suggest that 89% and 97% of patients randomised to EUROPA would have an incremental cost per QALY gained below £20 000 and £30 000, respectively.

Although this study is presented from the perspective of the UK NHS, the EUROPA study was a European trial involving patients from 24 countries. The model developed in this paper used health outcome and resource use information from the trial valued in UK pounds and used quality of life tariffs obtained from a sample of the UK population (Welsh Health Survey). Consideration of a simple adjustment for the UK suggested that the patients in the UK had a small, but statistically significant, reduction in resource use compared with patients in other European countries. Whether these results are directly transferable to other healthcare systems, such as the US, where patterns of resource use are known to differ, is less clear. Nevertheless, the results presented here are strongly suggestive that treatment with perindopril will reduce events and, therefore, the costs of treating those events. The recent decisions to license perindopril for the treatment of patients with stable coronary disease, on the basis of the EUROPA study, in both Europe and the US will increase the demand for evidence of cost effectiveness in different jurisdictions.

The results of the analysis emphasise the heterogeneity between patients in the cost effectiveness of perindopril. This is the result of variation in the risk of events in patients receiving standard management, not due to variation in the effect of perindopril, which is assumed to generate a 20% reduction in the risk of one or more primary events in all types of patient, according to the efficacy analysis in EUROPA.⁷ Risk equation 1 (table 1) is the key to understanding this heterogeneity, showing the patient characteristics which are estimated to increase risks and those estimated to be protective. Further consideration is needed about how those patients for whom treatment is most cost effective would be identified in routine clinical practice. In particular, it is worth considering that

patient groups in different jurisdictions may have different characteristics, but that the analysis presented here, by explicitly modelling the heterogeneity, provides a mechanism for adapting the results to a different patient population.

A recent cost-effectiveness analysis of the HOPE study concluded that ramipril was likely to be cost effective in high-risk patients, with a base case suggesting that treatment costs may be offset by the reduction in cost of treating events avoided.²⁵ This is consistent with the results reported here for a lower-risk population showing that, while not expected to be cost-saving, perindopril is likely to be associated with a favourable cost-effectiveness ratio for most patients in EUROPA. Recently, however, the PEACE Study investigators²⁶ reported the results of their comparison of placebo andtrandolopril 4 mg once a day in 8290 patients with overt coronary artery disease and preserved left ventricular systolic function. The study found no significant benefit from treatment, contrasting with the results of EUROPA (and, indeed, with those in higher-risk patients in the HOPE study^{3 25}). There may be several reasons for this discrepancy, including the comparatively lower dosage of drug used in the PEACE study than in EUROPA.

A limitation of this economic analysis is the fact that HRQL data were not collected in EUROPA. The estimation of QALYs is, therefore, partly based on external data and assumptions. Data were taken from the Welsh Health Survey using the SF-6D utility tariffs and adjusting for age, sex and history of angina or heart attack. The technical appendix (available at <http://heart.bmj.com/supplemental>) describes an alternative approach to quality adjustment, although this had no material effect on the estimated cost effectiveness. Treatment may sometimes be associated with side effects, but in the case of ACE inhibitor treatment, the impact of such side effects was assumed to be so low as to not affect quality of life. If side effects were to have an important impact on treatment they would probably result in treatment being stopped.

During the final stages of preparation of the analysis, an 11.8% price reduction in perindopril in the UK was announced as part of a general agreement between the UK Government and the Association of British Pharmaceutical Industries²⁷ aimed at reducing drug costs in the NHS. This price reduction took effect from 1 January 2005 and was independent of inflationary mechanisms. In presenting this analysis we chose to combine the most up-to-date perindopril price with the remainder of the costs estimated from 2003–4. Although it is common to present economic analyses in a single base year, the fact that the reduction of the price of perindopril is motivated by reasons different from inflation, adjusting to a common price base (that would have only increased the cost savings due to the use of perindopril) was not considered necessary.

An important uncertainty relates to how long patients would receive perindopril in routine practice. The primary analysis assumed that treatment would last for 5 years, based on experience in the EUROPA trial. As an alternative scenario, however, the cost effectiveness of lifetime use of the treatment was analysed. This results in added costs, but also additional QALYs and, overall, the cost effectiveness of lifetime treatment is similar to a 5-year intervention. This relationship between the cost effectiveness and duration of treatment is also relevant for compliance. Provided that non-compliance with treatment is also associated with a cessation in the cost of treatment, there is very little impact of compliance on cost effectiveness—patients not complying with treatment incur no costs of treatment, but receive no benefit.

In conclusion, the use of perindopril in people with stable coronary disease has been found to result in a gain in expected quality-adjusted survival duration, but also to increase costs.

Cost effectiveness varies with the risk characteristics of the patient, but 88% and 97% of patients randomised to EUROPA would have an incremental cost per QALY gained below £20 000 and £30 000, respectively.

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