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Summary

In 1998, the National Health Service (NHS) in England and Wales spent over £314 million on proton pump inhibitors (PPIs). The National Institute for Clinical Excellence (NICE) guidance on the use of PPIs in dyspepsia advises that the least expensive appropriate PPI be used. Consequently, the objective of this study was to assess the cost-effectiveness of all PPIs for the healing of reflux oesophagitis over 8 weeks from the perspective of the UK's NHS.

A decision analysis model was developed using healing rates derived from a systematic review of all PPIs using omeprazole as a common comparator. The economic analysis indicates that esomeprazole is cost-effective compared with all other PPIs currently available for healing reflux oesophagitis.

Key words: cost, economic, reflux oesophagitis, proton pump inhibitors, esomeprazole

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Introduction

Gastro-oesophageal reflux disease (GORD) is a prevalent condition commonly managed in a primary care setting. In the UK, up to 40% of the adult population may suffer from dyspepsia in any given year, of whom up to 25% can be categorised as having GORD[1]. Furthermore, studies have demonstrated that GORD symptoms significantly interfere with a patient's normal activities and impairs their health-related quality of life[2–4]. Although there are many treatment options available, proton pump inhibitors (PPIs) are currently the most effective treatment for GORD[5].

The appropriate prescribing of PPIs for the treatment of GORD is of interest to all healthcare budget holders. In the UK, PPI prescribing accounts for the largest spend for a class of drugs in the unified drug budget controlled by primary care organisations. In 1998, total PPI spend for the NHS in England and Wales was in excess of £314 million[1].

The appraisal of PPIs in dyspepsia by the National Institute for Clinical Excellence (NICE) recommends that the optimal dose of PPI should be used in healing and once healing is achieved this should be stepped down to the lowest dose to maintain symptom relief. The guidance advises that the "least expensive appropriate PPI should be used"[1].

There has been considerable confusion over the relative efficacies of the licensed healing doses of PPIs available in the UK and so the ability of individual clinicians to adhere to NICE guidance is limited. Several attempts have been made to clarify this confusion by systematic review and meta-analysis[6–8]. However, most of these reviews have either compared all PPIs with all H_2-receptor antagonists (i.e. drug class versus drug class), or else only compared two PPIs.

The NICE appraisal process was completed prior to the introduction of the new PPI, esomeprazole. It is possible that the NICE guidance on PPIs in dyspepsia may have been different had data on esomeprazole been available at the time of appraisal.

In acid suppression studies, esomeprazole has been shown to maintain intra-gastric pH above 4 for significantly longer than lansoprazole, omeprazole, pantoprazole or rabeprazole, which may correlate with higher healing rates in reflux oesophagitis[9,10]. However, these studies cannot replace direct comparison in clinical trials.

A recent systematic review was conducted comparing all PPIs in the healing of reflux oesophagitis using omeprazole as a common comparator[11]. Omeprazole was chosen as the common comparator because it is the most common PPI that is used in clinical trials with other PPIs and provides the largest pool of comparable trials for review. The systematic review used endoscopic healing of oesophagitis at 4 and 8 weeks for efficacy comparison in preference to symptom relief, as the latter is not assessed consistently from study to study while the former can be objectively evaluated. The systematic review

Table 1. Relative risk for UK healing doses of PPIs compared to omeprazole 20 mg from a systematic review of all PPI in the healing of reflux oesophagitis[11] (95% confidence intervals given in parentheses)

	Relative risk	
PPI	*4 weeks*	*8 weeks*
Esomeprazole 40 mg	1.14 (1.10 – 1.18)	1.08 (1.05 – 1.10)
Lansoprazole 30 mg	1.02 (0.97 – 1.08)	1.01 (0.97 – 1.06)
Pantoprazole 40 mg	0.99 (0.91 – 1.07)	0.98 (0.93 – 1.04)
Rabeprazole 20 mg	1.00 (0.87 – 1.14)	0.98 (0.91 – 1.05)

concluded that only esomeprazole has significantly greater healing rates at 4 and 8 weeks than omeprazole.

In today's NHS prescribing decisions are rarely made on efficacy alone. The budgetary impact must also be considered. This current work sets out to establish which PPI is the most cost-effective treatment option for the healing of reflux oesophagitis based on the best available efficacy data derived from the systematic review.

Methods

Effectiveness

The meta-analysis from the systematic review of PPIs in the healing of reflux oesophagitis provides summary estimates for esomeprazole, lansoprazole, pantoprazole and rabeprazole compared with omeprazole[11]. The summary estimate used is relative risk, also known as the risk ratio. That is, the probability of being healed by the PPI divided by the probability of being healed by omeprazole. The general formula for calculating relative risk[12] is given below:

$$RR = EER / CER$$

Where: RR, Relative Risk; EER, Experimental Event Rate; CER, Control Event Rate.

The systematic review provides relative risks for the healing at 4 and 8 weeks (Table 1). In order to convert the relative risks from the systematic review into healing rates that can populate the decision analysis model, we need to have a reliable estimate of the healing rates for omeprazole at 4 and 8 weeks. The largest comparable trials involving omeprazole from the systematic review are the trials comparing omeprazole with esomeprazole. When the healing rates are pooled for omeprazole from these trials they provide healing rates of 65.1% and 82.2% at 4 and 8 weeks respectively.

The healing rates for the other PPIs cannot be simply pooled in this manner as it would lose the richness of the meta-analysis and the robustness of using a common comparator to make the healing rates comparable.

Using the omeprazole healing rates we can convert the relative risks produced by the

Table 2. Calculated healing rates for UK healing doses of PPIs derived from the systematic review (95% confidence intervals given in parentheses)

	Healing rates	
PPI	*4 weeks*	*8 weeks (cumulative)*
Omeprazole 20 mg	65.1%[a]	82.2%[a]
Esomeprazole 40 mg	74.2% (71.6 – 76.8)	88.8% (86.3 – 90.4)
Lansoprazole 30 mg	66.4% (63.1 – 70.3)	83.0% (79.7 – 87.1)
Pantoprazole 40 mg	64.4% (59.2 – 69.7)	80.6% (76.4 – 85.5)
Rabeprazole 20 mg	65.1% (56.6 – 74.2)	80.6% (74.8 – 86.3)

[a]95% Confidence Intervals cannot be calculated for the omeprazole healing rates as these values are calculated from a pooled analysis.

meta-analysis in the systematic review into healing rates (Table 2) by transforming the general formula for calculating relative risk to elicit experimental event rates:

$$EER = RR \times CER$$

An example of this calculation for converting the 4-week relative risk of esomeprazole compared to omeprazole into a healing rate is given below:

Healing rate for esomeprazole 40 mg at 4 weeks	=	Relative risk for esomeprazole 40 mg at 4 weeks	*	Healing rate for omeprazole 20 mg at 4 weeks
	=	1.14	*	0.651
	=	0.742 or 74.2%		

The decision analysis model also requires the 8-week healing rate data to be the additional probability of being healed at 8 weeks if not healed at 4 weeks, rather than the cumulative rate of healing over 8 weeks (Table 3). This can be calculated as follows: cumulative probability of being healed at 8 weeks – probability of being healed at 4 weeks/1 – probability of being healed at 4 weeks.

Table 3. Additional healing rates at 8 weeks if not healed at 4 weeks for UK healing doses of PPIs derived from the systematic review (95% confidence intervals given in parentheses)

PPI	*Healing rates 8 weeks (additional)*
Omeprazole 20 mg	49.0%[a]
Esomeprazole 40 mg	56.5% (51.8 – 58.7)
Lansoprazole 30 mg	49.5% (45.0 – 56.7)
Pantoprazole 40 mg	45.3% (42.2 – 52.2)
Rabeprazole 20 mg	44.3% (41.9 – 46.9)

[a] 95% confidence intervals cannot be calculated for the omeprazole healing rates as these values are calculated from a pooled analysis.

Table 4. Resource unit costs at 1999/2000 prices

Item	*Price (GBP)*	*Source*
Esomeprazole 20 mg	18.50	BNF, Sept 2000[13]
Esomeprazole 40 mg	28.56	BNF, Sept 2000[13]
Lansoprazole 15 mg	12.98	BNF, Sept 2000[13]
Lansoprazole 30 mg	23.75	BNF, Sept 2000[13]
Omeprazole 10 mg	18.91	BNF, Sept 2000[13]
Omeprazole 20 mg	28.56	BNF, Sept 2000[13]
Pantoprazole 20 mg	12.88	BNF, Sept 2000[13]
Pantoprazole 40 mg	23.65	BNF, Sept 2000[13]
Rabeprazole 10 mg	12.43	BNF, Sept 2000[13]
Rabeprazole 20 mg	22.75	BNF, Sept 2000[13]
Endoscopy[a]	318.72	Bate and Richardson, 1994[14]
GP visit	23.00	Netten and Curtis, 2000[15]
GP visit (healed)	17.00	Netten and Curtis, 2000[15]
Outpatient visit	74.38	CIPFA Health Database, 2000[16]

All PPI prices = 28 days medication.

[a] Price inflated from 1991 prices using the pay and price HCSC inflation index.

An example of calculating the additional healing rate at 8 weeks if not healed at 4 weeks for esomeprazole compared to omeprazole is given below (example is shown to 3 decimal places for illustrative purposes):

= (0.888 – 0.742)/(1 – 0.742)
= 0.565 or 56.5%

Costs

This study compares the direct healthcare costs and consequences, from the perspective of the UK National Health Service (NHS). Resource units were multiplied by the national published resource costs at 1999/2000 prices (Table 4).

Decision analysis model

A simple decision analysis model was constructed using Treeage DATA™ 4.0 to compare the cost-effectiveness of all PPIs currently licensed in the UK for the healing of endoscopically confirmed reflux oesophagitis (Figure 1). The model depicts the sequential management of reflux oesophagitis based on the results of a survey of UK general physicians and gastroenterologists on the longitudinal management of a typical reflux oesophagitis patient[17]. Hence, following an initial visit to their GP, patients are prescribed a 4-week course of the UK licensed healing dose of omeprazole 20 mg, esomeprazole 40 mg, lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg od. All patients are seen by their GP after 4 weeks. Patients who remained unhealed after 4-weeks treatment are prescribed an additional 4-week course of the same PPI at the same dose, after which a further follow-up visit was made.

Figure 1. Decision analysis model for the acute treatment of reflux oesophagitis over 8 weeks

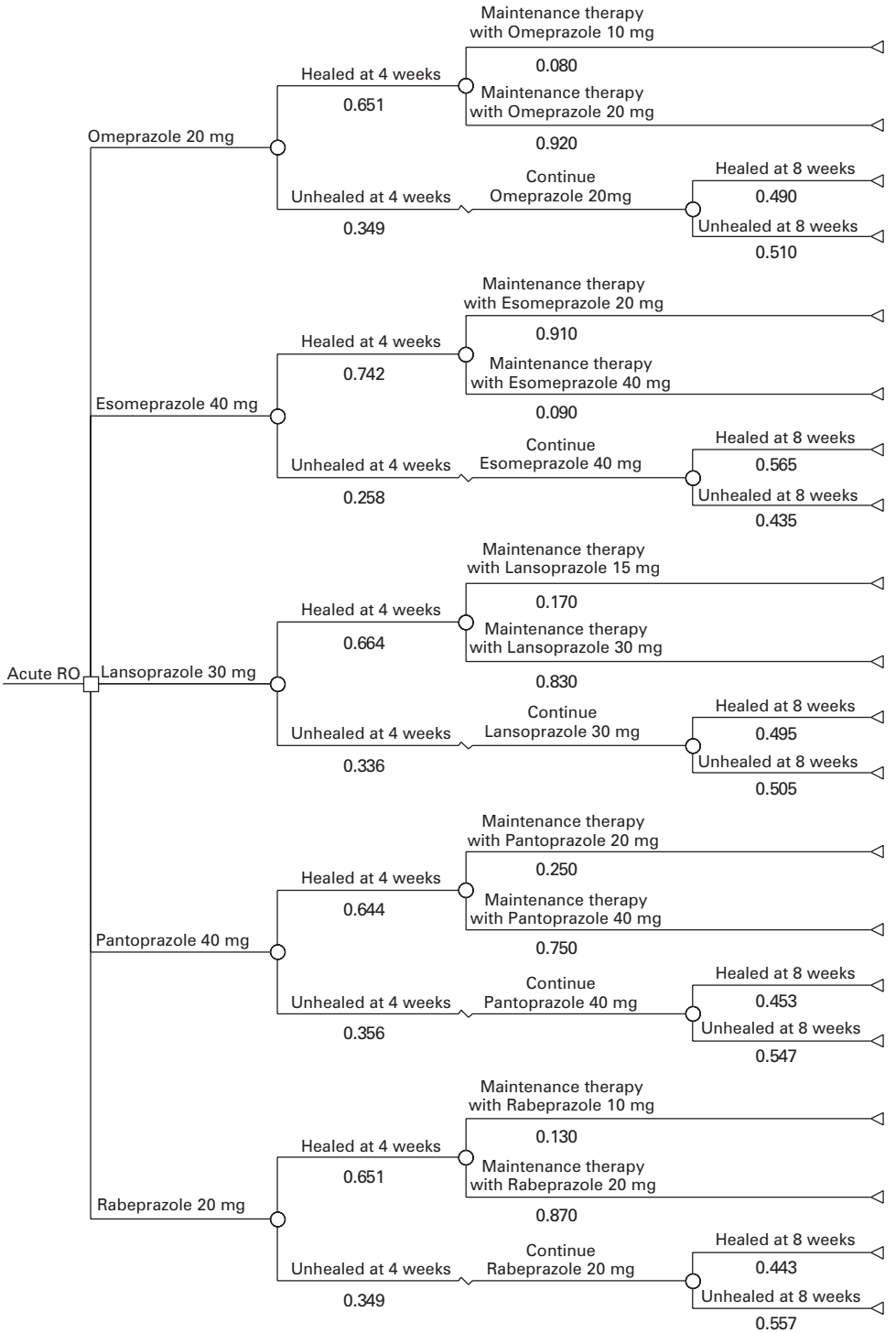


Table 5. Probability of high- or low-dose maintenance therapy

PPI	*Low-dose*	*High-dose*
Omeprazole	0.08	0.92
Esomeprazole	0.91	0.09
Lansoprazole	0.17	0.83
Pantoprazole	0.25	0.75
Rabeprazole	0.13	0.87

Approximately 10% of unhealed patients are referred to a gastroenterologist and 10% are referred for upper gastrointestinal endoscopy. The latter includes patients directly referred for endoscopy from primary care as well as some of the those referred to a gastroenterologist.

In line with NICE guidance[1], healed patients should continue treatment with a PPI at the lowest maintenance dose that provides symptom relief. An analysis by AstraZeneca of the Mediplus® UK primary care database (IMS Health Ltd) (AstraZeneca, data on file, NEX/068/Feb 2002) indicates that not all patients are switched to a low-dose of PPI for maintenance therapy. Consequently, a PPI specific probability of switching to maintenance therapy, as determined by current UK treatment practice is included in the model (Table 5). Data relating to the probability of switching to low- or high-dose maintenance therapy in the esomeprazole arm of the model was not obtained from Mediplus® as esomeprazole has not been available to clinicians long enough for sufficient data to be collected. Instead the data were obtained from an audit of eight general practices where patients who switched to low-dose esomeprazole were reviewed after 3 months to discover what proportion were still receiving low-dose maintenance therapy (AstraZeneca, data on file, NEX/067/Jan2002).

Cost-effectiveness analysis

In this analysis, the measure of clinical effectiveness is "the proportion of patients healed at 8 weeks". Hence, the model was used to estimate omeprazole's incremental cost-effectiveness compared to the alternative PPIs, calculated as:

$$\text{Additional cost per additional patient healed at 8 weeks} = \frac{\text{Difference in cost of resource use between treatment strategies}}{\text{Difference in number of patients healed at 8 weeks between treatment strategies}}$$

Sensitivity analysis

A sensitivity analysis was conducted to assess the robustness of the cost-effectiveness analysis by simultaneously varying key model parameters using a Monte Carlo simulation of 1,000 patients. As the healing rates were derived from the relative risks provided by the meta-analysis, standard deviations could not be calculated for the healing rates. Instead, triangular distributions were applied to the 4- and 8-week healing rates. The 95% confidence intervals for the healing rates were estimated from the systematic review using the same methods described in the effectiveness section and used to define the limits of the triangular distributions. Moreover, triangular distributions were applied to the probability of switching to maintenance therapy if healed at 4 weeks,

Table 6. Cost-effectiveness of PPIs compared to omeprazole in the healing of reflux oesophagitis

Strategy	*Mean cost per patient (C)*	*Incremental cost per patient (ΔC)*	*Effect (E)*	*Incremental Effect (ΔE)*	*Mean cost per patient healed (C/E)*	*ICER (ΔC/ΔE)*
Omeprazole	117.02		0.822		142.36	
Esomeprazole	106.73	–10.29	0.888	0.066	120.19	Dominant
Lansoprazole	107.43	–9.59	0.830	0.008	129.43	Dominant
Pantoprazole	108.70	–8.32	0.806	–0.016	134.86	£520.00
Rabeprazole	108.59	–8.43	0.806	–0.016	134.73	£526.88

the probability of being referred to a gastroenterologist and the probability of undergoing endoscopy. Upper and lower limits were set at ± 10% which equates to a relative difference of ± 100%.

Results

Table 6 presents the mean expected per patient cost of healing reflux oesophagitis over 8 weeks, stratified by PPI, and the corresponding treatment outcomes. Omeprazole 20 mg is the most costly treatment option, whereas esomeprazole 40 mg is the least expensive. Although, there is a higher probability of being healed at 8 weeks with omeprazole compared to pantoprazole 40 mg and rabeprazole 20 mg, the mean cost per patient healed remains the highest. Moreover, the incremental cost effectiveness ratio (ICER) indicates that each additional patient healed with omeprazole compared to pantoprazole 40 mg and rabeprazole 20 mg costs an additional £520.00 and £526.88 respectively.

The results show that esomeprazole 40 mg dominates omeprazole 20 mg, that is, mean values indicate that it is more effective and less costly. Lansoprazole 30 mg is also considered dominant compared to omeprazole 20 mg, however the mean difference in effect being only 0.8% is unlikely to be clinically significant. Furthermore, a direct comparison of the two treatment options (Table 7) reveals that lansoprazole 30 mg is subsequently dominated by esomeprazole 40 mg. However, although there is a relatively large difference in effect (0.058) the overall difference in costs (£0.77) is marginal, suggesting the most likely scenario is that the two treatment options are cost neutral. Nevertheless, the mean cost per patient healed with esomeprazole 40 mg is £9.32 lower than lansoprazole 30 mg.

Table 7. Cost-effectiveness of esomeprazole compared to lansoprazole in the healing of reflux oesophagitis

Strategy	*Mean cost per patient (C)*	*Incremental cost per patient (ΔC)*	*Effect (E)*	*Incremental Effect (ΔE)*	*Mean cost per patient healed (C/E)*	*ICER (ΔC/ΔE)*
Esomeprazole	106.73		0.888		120.19	
Lansoprazole	107.43	0.70	0.830	–0.058	129.43	Dominated

Table 8. Expected mean costs of the treatment components attributable to managing reflux oesophagitis over 8 weeks (percentage of total expected cost in parentheses)

Resource use category	*PPI*									
	Omeprazole		*Esomeprazole*		*Lansoprazole*		*Pantoprazole*		*Rabeprazole*	
Drug	56.96	(48.7)	50.97	(47.8)	46.78	(43.5)	46.09	(42.4)	45.10	(41.6)
GP	49.09	(41.9)	47.10	(44.1)	49.39	(46.0)	50.32	(46.3)	50.72	(46.7)
Outpatient referral	2.07	(1.8)	1.64	(1.5)	2.13	(2.0)	2.33	(2.1)	2.42	(2.2)
Endoscopy	8.90	(7.6)	7.02	(6.6)	9.13	(8.5)	9.96	(9.2)	10.35	(9.5)
Total	117.02	(100)	106.73	(100)	107.43	(100)	108.70	(100)	108.59	(100)

Table 8 illustrates that drug acquisition costs are the largest component of the overall cost of treatment in the omeprazole and esomeprazole arms of the model accounting for 48.7% and 47.7% respectively, reflecting their relatively high unit cost compared to the other PPIs. Conversely, GP consultations represent the highest single cost with lansoprazole, pantoprazole and rabeprazole arms. However, it is worth noting that the differences between drug acquisition cost and GP consultations are almost negligible across all of the PPIs assessed. Not surprisingly, the cost of referral to a gastroenterologist and clinical investigation via endoscopy increase in line with the relative efficacy of the PPIs, with esomeprazole having the lowest secondary care cost and rabeprazole the highest.

The Monte Carlo simulation undertaken as a sensitivity analysis (Table 9) indicates that the mean expected per patient costs were relatively robust to changes in key model parameters. However, with the

Table 9. Monte Carlo simulation, descriptive statistics

	Mean	*SD*	*Min*	*Max*	*Median*	*2.5%*	*97.5%*
Cost (GBP)							
Omeprazole	119.45	1.40	115.85	122.92	119.48	116.68	122.06
Esomeprazole	107.16	1.34	103.57	111.38	107.15	104.67	109.78
Lansoprazole	108.14	1.67	103.02	113.04	108.09	105.07	111.44
Pantoprazole	108.88	2.08	102.85	114.85	108.84	104.99	112.98
Rabeprazole	107.50	2.68	100.13	116.40	107.37	102.51	112.86
Effect							
Omeprazole	0.822	0.000	0.822	0.822	0.822	0.822	0.822
Esomeprazole	0.886	0.006	0.869	0.900	0.886	0.874	0.898
Lansoprazole	0.835	0.011	0.804	0.867	0.835	0.814	0.855
Pantoprazole	0.810	0.013	0.771	0.846	0.811	0.784	0.836
Rabeprazole	0.807	0.020	0.753	0.855	0.807	0.768	0.846

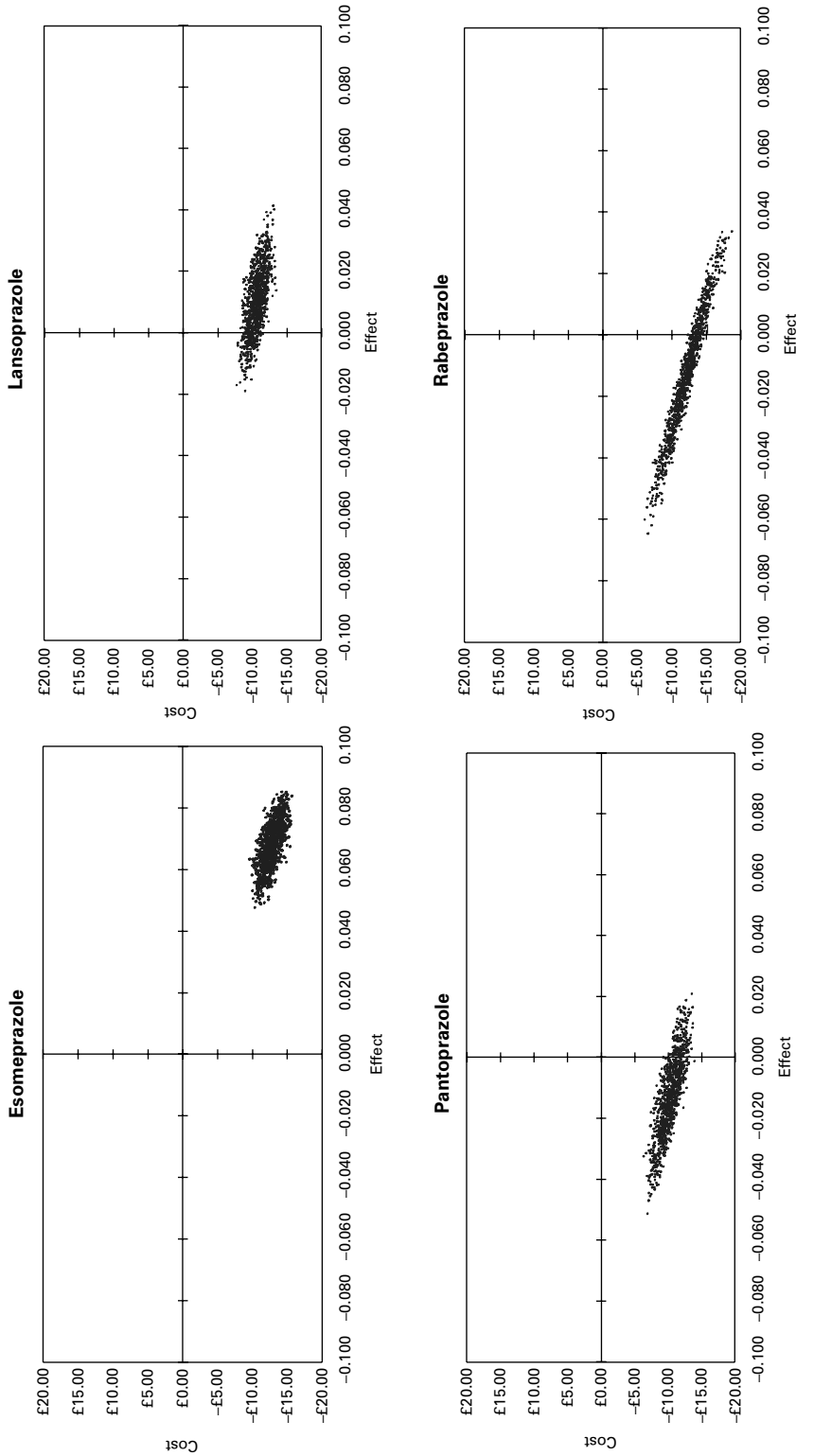


Figure 2. Cost-effectiveness quadrants comparing PPIs with omeprazole

exception of esomeprazole, the expected mean number of patients healed at 8 weeks was sensitive to changes in healing rates. Specifically, the upper and lower boundaries within which 95% of the 1,000 model iterations lie for omeprazole, lansoprazole, pantoprazole and rabeprazole overlap in terms of effect. Figure 2 illustrates a series of cost-effectiveness quadrants comparing each of the newer PPIs with omeprazole 20 mg. A data point above the horizontal axis would indicate that the mean expected cost per patient for that individual model iteration was higher for the comparator PPI compared to omeprazole 20 mg (i.e. the comparator PPI is more expensive than omeprazole 20 mg). Conversely, a data point below the horizontal axis would indicate the comparator PPI was less expensive than omeprazole 20 mg. Likewise, a data point to the right of vertical axis would indicate that for that individual model iteration, more patients were healed with the comparator PPI than with omeprazole (i.e. the comparator is more effective than omeprazole 20mg). Whereas, a data point to the left of the vertical axis would indicate that the comparator PPI was less effective than omeprazole 20 mg. Clearly, the healing of reflux oesophagitis with the newer PPIs is less expensive than with omeprazole over 8 weeks. However, esomeprazole 40 mg is the only PPI that is both more effective and less costly than omeprazole 20 mg.

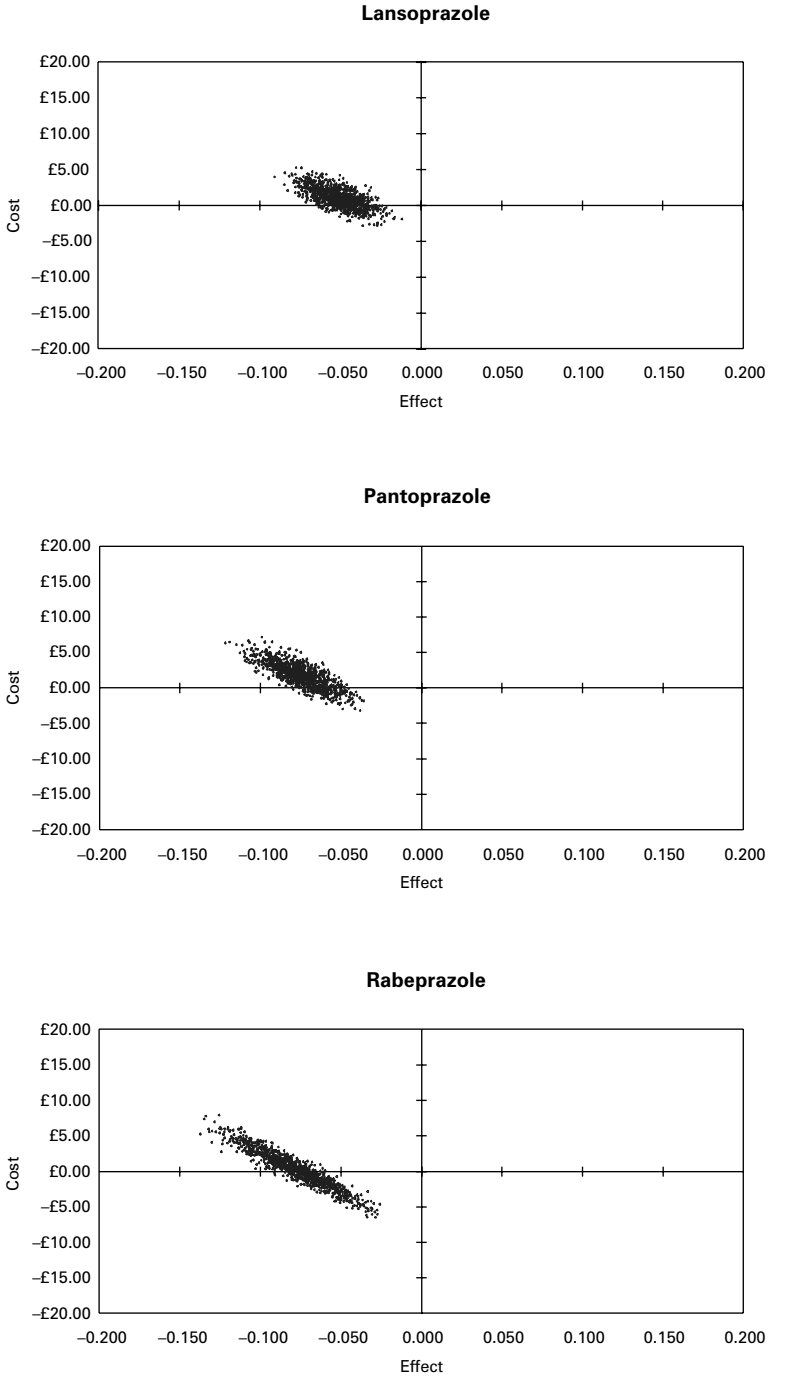
In response to the finding that esomeprazole 40 mg is the only PPI to dominate omeprazole, further cost-effectiveness quadrants were generated using esomeprazole as the common comparator (Figure 3). Clearly, the Monte Carlo simulation data supports the view that in terms of cost, lansoprazole 30 mg, pantoprazole 40 mg and rabeprazole 20 mg are relatively cost neutral compared with esomeprazole 40 mg despite the higher acquisition cost of esomeprazole. However, none of the scatterplots cross-over the vertical axis indicating that esomeprazole 40 mg does have an efficacy advantage over all of the other PPIs.

Discussions

With the increasing emphasis on adherence to NICE guidance, healthcare professionals should be aware of the clinical and economic impact of using PPIs in the healing of reflux oesophagitis. Accordingly, we performed a cost-effectiveness analysis to determine the expected direct healthcare costs and consequences associated with this prevalent condition.

The current study indicates that treatment with esomeprazole is not only more effective in the healing of reflux oesophagitis, but also less costly than omeprazole. The effectiveness advantage over omeprazole transfers into potential cost savings for the NHS. Furthermore, if costs are similar, the more effective treatment is also considered cost-effective, since better effectiveness is provided at similar costs. With this in mind, the present study indicates that the healing of reflux oesophagitis with esomeprazole, lansoprazole, pantoprazole and rabeprazole is more cost-effective than treatment with omeprazole over 8 weeks. However, the

Figure 3. Cost-effectiveness quadrants comparing esomeprazole with lansoprazole, pantoprazole and rabeprazole



study also demonstrates that despite its higher acquisition cost, esomeprazole is more cost-effective than lansoprazole, pantoprazole and rabeprazole.

To compare the efficacies of the PPIs available in the UK in the healing of reflux oesophagitis we would ideally look to a large randomised controlled trial comparing all five PPIs over an 8-week period. However, such a trial has not been carried out and the expense of running such a large trial makes it unlikely that it will ever be carried out. The systematic review[11] comparing esomeprazole, lansoprazole, pantoprazole and rabeprazole with omeprazole is likely to be the closest approximation to this hypothetical trial, which is why it was used as the basis for the current study.

Individual comparisons of different PPIs with each other have been undertaken. The majority of these comparisons have been a single PPI compared with omeprazole and the richness of this data is captured in the systematic review.

The systematic review shows that esomeprazole is the only PPI to have higher healing rates than omeprazole at 4 and 8 weeks and so infers superior efficacy of esomeprazole compared to lansoprazole, pantoprazole and rabeprazole. The higher healing and maintenance rates of esomeprazole compared to lansoprazole have been shown in direct comparison[18, 19] but studies comparing esomeprazole with pantoprazole or rabeprazole have yet to be carried out.

There are a number of limitations to this study. Our decision-analytic model only assesses the healing phase of what is a chronic disease. Moreover, the analysis does not include the management of those patients who remain unhealed at 8 weeks. It is likely that treatment costs in terms of drugs, referrals, investigations and procedures are high for these patients. This positively biases the results in favour of the less effective PPIs since they would incur higher additional treatment costs than the esomeprazole strategy. Ideally, the analysis would have also used a uniform data source for each of the comparable treatment options, however this was unavailable in the case of the proportion of patients healed at 4 weeks who switched to low dose maintenance therapy. Clearly, the decision model should be updated as and when more robust data becomes available.

Conclusion

Esomeprazole is cost-effective compared with all other currently available PPIs in the healing of reflux oesophagitis over 8 weeks, since esomeprazole provides a significantly better effectiveness at similar or lower treatment costs. The higher healing rate at 4 weeks observed with esomeprazole compared to other PPIs results in fewer patients requiring a second healing course rather than switching to a potentially less expensive maintenance dose.

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