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Economic Evaluations of Gastroesophageal Reflux Disease Medical Management: A Systematic Review

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SUMMARY

Background—Gastroesophageal reflux disease (GERD) contributes to substantial medication use and costs worldwide. Economic evaluations provide insight into the value of healthcare, taking into account cost, quality, and benefits of particular treatments.

Aims—Our aims were to systematically review the existing literature to identify economic evaluations of GERD management strategies, to assess the scientific quality of these reports and to summarize the economic outcomes of these evaluations.

Methods—We identified economic evaluations and cost studies of GERD management strategies by searching PUBMED and the NHS economic evaluation database *via* the Cochrane library. Searching was restricted to articles in English language journals from July 2003 to July 2013. Cost identification articles were excluded from the final analysis.

Results—Eighteen articles were included in the final analysis; 61% of these met all criteria for quality reporting. Overall, proton pump inhibitor (PPI) therapy was preferred (most effective and least costly) as empiric therapy for patients with reflux symptoms, except in patient populations with high *H. pylori* prevalence (>40%). Initial empiric PPI therapy (*vs*. initial endoscopy stratification or *H. pylori* testing) is the most cost-effective initial strategy for patients with typical GERD symptoms. Surgery may be cost-effective in patients with chronic GERD symptoms at time horizons of 3–10 years. Endoscopic anti-reflux procedures were not cost-effective based on available data.

Conclusions—Further economic evaluations should adhere to standard reporting measures of cost estimates and outcomes, and should attempt to account for and compare the large heterogeneity of patient phenotypes and treatment effects seen with anti-reflux therapies.

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Declaration of Interests

Drs. Gawron and French have no outside interests to declare.
Dr. Pandolfino has served as a consultant for Given Imaging.
Dr. Howden has served as a consultant and speaker for Takeda, Otsuka, Ironwood and Forest and as a speaker for GlaxoSmithKline International.

Keywords

GERD; proton pump inhibitors; health economics

INTRODUCTION

Gastroesophageal reflux disease (GERD) symptoms and sequelae cause considerable morbidity and contribute to substantial medication use and costs worldwide [1,2]. In the United States (US) alone, overall spending on all GI diseases is estimated to be $142 billion (in 2009 US dollars) per year in direct and indirect costs [3]. GERD accounts for approximately $15–20 billion of these direct and indirect costs [4]. A study in 1997 found that total unadjusted medical costs of GERD in a US health maintenance organization population (1550 people with GERD) were $2089 higher than for controls; this corresponded to around $471 in attributable costs [5]. Factors contributing to GERD-related costs include direct costs (*e.g.*, medication use, diagnostic testing, physician visits, and hospitalizations) and indirect costs (*e.g.*, decreased quality of life, work absenteeism, and loss of productivity). It has been estimated that prescribed medications for GERD, primarily proton pump inhibitors (PPIs), account for over 50% of prescriptions for all digestive diseases, resulting in around $10 billion in annual direct health care costs [1,4]. In 2010, one PPI (esomeprazole) accounted for the most retail dollars (>$5.2 billion) out of all branded drugs sold in the US [6].

In light of the enormous healthcare burden attributed to GERD, numerous studies have evaluated cost, healthcare utilization, and cost effectiveness of differing management strategies. As economic evaluations are often used as the basis for practice guidelines and resource allocation, it is critical that reporting of data is appropriately scrutinized. The growing field of comparative effectiveness research also often uses cost considerations to determine thresholds of effectiveness. Recently, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) developed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to guide quality reporting in economic evaluations [7].

Our first objective was to systematically evaluate the existing literature to identify economic evaluations of GERD medical management strategies and assess the scientific quality of these reports using the CHEERS guidelines. Our second objective was to summarize the economic outcomes of the included studies.

METHODS

We identified economic evaluations and cost studies of GERD medical management strategies by searching PUBMED and the National Health Service (NHS) economic evaluation database *via* the Cochrane library. Searching was restricted to articles in English language journals from July 2003 to July 2013. The search strings for both databases were as follows:

PUBMED—(((((((“cost-benefit analysis”[MeSH Terms] OR cost benefit[Text Word])) OR (cost effectiveness analysis)) OR (cost minimization analysis)) OR (“costs and cost analysis”[MeSH Terms] OR cost analysis[Text Word])) OR (“Quality-Adjusted Life Years” [Mesh] OR QALY[Text Word]))) AND ((((heartburn) OR “Gastroesophageal Reflux” [Mesh]) OR GERD) OR gastroesophageal reflux disease)

NHS economic evaluation database (Cochrane library): gastroesophageal reflux disease (MeSH and keyword) then limited to economic evaluations

Inclusion/Exclusion criteria

Abstracts from the articles identified by the initial search strategy were then analyzed for inclusion or exclusion as follows:

Inclusion criteria—Adult studies addressing management strategies for GERD in English language journals were included; studies comparing medical to surgical management were also included. A study was included in the final analysis if it was considered to be an *economic evaluation*; that is, if it reported evidence on costs and endpoints for effectiveness or benefits.

Exclusion criteria—Publications focused on Barrett’s esophagus, diagnostic testing, only surgical or endoscopic therapy for GERD, dyspepsia, editorials, comments, letters to the editor, news, conference abstracts, and material published prior to 2003 were excluded from the analysis. Pediatric studies were also excluded. Cost identification articles were excluded from the final analysis of quality and outcomes. A study was considered a *cost identification analysis* if cost data were presented but were not related to the treatment effectiveness or benefits.

Review of methodological quality and outcomes of economic evaluations

Included studies were assessed according to the CHEERS task force guidelines on good reporting practices for economic evaluations by two independent reviewers (AJG, DDF) [7]. The CHEERS checklist has been provided in appendix A. Data for the economic evaluations were then abstracted and summarized according to the population studied and cost outcomes.

RESULTS

The initial literature search identified 219 and 52 articles from PubMed and the Cochrane/NHS economic evaluation database, respectively (Figure 1). After exclusion criteria were applied and the results were combined, the abstracts and manuscripts (if necessary) of 58 articles were reviewed for initial inclusion in the final review. Of these, 35 (60%) were excluded as they reported cost identification outcomes without linking cost to effectiveness. An additional six articles were subsequently excluded as they did not involve any comparisons of the medical management of GERD (n=4) or focused only on screening for Barrett’s esophagus (n=2). One additional article was obtained *via* expert opinion that

was not identified with the literature search [8]. Thus, eighteen articles were included in the final analysis [8–25] (Figure 1); their general characteristics are shown in Table 1.

The quality of the eighteen articles, as assessed by the CHEERs guidelines is shown in Table 2. Of the 24 items, 11 articles (61%) met all criteria for economic evaluation reporting [8–15,18,19,21]. Only one did not explicitly identify the study as an economic evaluation in the title [16]. The majority of missing items were specific methods including mention of discount rates (n=4) [16,23–25] and study parameters (n=2) [16,25]. Three articles did not disclose funding sources [22–24] and four did not disclose conflicts of interest [17,20,22,23]. Of these, two included neither disclosure of funding nor conflicts of interest [22,23].

Of the eighteen included articles (Table 3), three used a decision analysis [18,22,24] nine used Markov modeling [9,10,12–14,17,20,21,23] and five our reported cost outcomes related to randomized trials [8,11,15,16,19]. Only one used a retrospective cohort design in assessing the incremental annualized healthcare costs of compliant and non-compliant PPI users [25]. Fifteen articles (78%) included comparisons of different PPI strategies (n=7, [16–21,23]) or PPI therapy with surgery (n=8, [8–15,24]). Four articles compared PPI therapy with endoscopic-based management (either as a diagnostic or therapeutic strategy) [9,16,17,22]. Of the twelve papers that used decision analysis or Markov models [9,10,12–14,17,18,20–24], nine were performed from a non-US societal or public health system perspective [9,12–14,17,20,21,23,24]. The majority of articles (n=15) used a public healthcare system perspective (*e.g*. UK NHS, US Medicare) [9–17,19–23,26]. One study used an employer cost perspective [18], one used a societal perspective [24], and one used a third party payer perspective [25]. More articles reported cost outcomes in US dollars (n=7) than other individual currencies (Table 1). The time horizons used in the decision and Markov models were highly variable ranging from five months [23] to a lifetime [8,13,14].

The economic outcomes for specific articles are summarized in Table 3; most studies reported outcomes as incremental cost effectiveness ratios (ICERs).

PPI therapy vs. surgery

Of the articles comparing PPI therapy to laparoscopic surgery, surgery was cost-effective when compared to long term PPI therapy (ranging from 3 years to lifetime). For example, in the study by Goeree *et al* [15] laparoscopic Nissen fundoplication (LNF) had a primary outcome ICER of $29,404 per quality of life year (QALY) gained when compared to PPIs over a 3-year time horizon. However, this study's outcomes were very sensitive to QALY estimates. For example, using EQ-5D utility weights resulted in an ICER of 76,310/QALY (LNF *vs*. PPIs). When a lifetime perspective was applied by Epstein *et al*., LNF had an ICER of $4385/QALY compared to PPI therapy [12]. However, modeling was based on only one year of data from the REFLUX trial and relied on assumptions of surgery durability [12]. The most recent study by Grant *et al*. used 5 year follow up data from the REFLUX trial which is a major strength compared to older studies that relied on assumptions of surgical durability [8]. They found that although initially more costly, surgery is more likely to be cost-effective as it provides better relief of GERD symptoms and improved quality of life.

One study reported that PPI therapy was more effective and less costly compared to surgery at a 10 year time horizon [10]. It should be noted that this study's outcomes were sensitive to QALY estimates which were primarily derived from patients who had open (as opposed to laparoscopic) fundoplication. Also, the probability estimates of symptom recurrence after surgery were derived from an older paper evaluating outcomes of Toupet fundoplication which showed 67% recurrence of symptoms within three years of surgery [27].

PPI therapeutic regimen comparisons

In studies comparing different PPI therapeutic regimens, results differed based on the setting and comparisons. Moayyedi *et al* found that empiric PPI therapy based on a structured questionnaire was cost-effective ($764/quality adjusted life month (QALM) gained) compared to controls [19]. In an extensive Markov model evaluating seven different PPIs and a variety of treatment regimens, generic omeprazole (20–40mg daily) was the least costly and most effective, and hence dominated all strategies [21]. Rabeprazole was also found to be cost-effective compared to other PPIs (except omeprazole) with £3.42 per symptom-free day [21].

Empiric PPI therapy vs. endoscopic directed medical therapy or H. pylori testing

Empiric esomeprazole therapy was found to be less costly per treated patient using data from a randomized trial comparing empiric PPI therapy (€88.34) and PPI treatment based on endoscopy (€127.06) [16]. In particular, the authors noted that empiric treatment saved €38.72 per patient and could reduce the number of endoscopies by ~90% [16]. *H. pylori* prevalence was not determined in the trial [16]. In a population with high background prevalence of *H. pylori* infection (base case estimate of 46%), You *et al* determined that empiric PPI therapy cost more ($2158/QALY) than an initial test and treat strategy for *H. pylori (*$1778/QALY) or early endoscopy ($1797/QALY) compared to no therapy [17]. However, empiric PPI therapy was overall more effective as it resulted in the highest number of symptom-free patient-years as it can also improve dyspeptic symptoms associated with *H. pylori* infection [17].

PPI therapy vs. endoscopic therapy

One study was identified that compared PPI therapy to endoluminal plication (Endocinch™) or radiofrequency coagulation for GERD (Stretta™ procedure); PPI therapy was dominant (*i.e*., less costly and more effective) regardless of time as long as the cost of PPI therapy was below $140/month or the cost of endoscopic therapy was over $3400 [22].

PPIs vs. H_2-receptor antagonists (H_2RAs)

Two studies compared PPI with H_2RA treatment. Habu *et al* developed a Markov model comparing initial PPI therapy and H_2RA with escalating PPI therapy in patients with endoscopically-confirmed reflux esophagitis *vs*. no therapy [23]. Compared to no therapy, initial PPI therapy had an ICER of ¥211/day without esophagitis. This was less costly (and more effective) than first using an H_2RA (¥217/day without esophagitis compared to no intervention). Thresholds for cost-effectiveness were not reported in the paper by Habu *et al*. You *et al* also used Markov modeling to evaluate standard dose PPI therapy with low-dose

PPI and standard dose H_2RA therapy for healed esophagitis [20]. Standard dose PPI therapy was less costly per QALY gained ($905) compared to low-dose PPI ($1374/) and H_2RA treatment ($1633) [20]. The results were due to a lower relapse probability with more potent therapy (*i.e.* standard dose PPI) leading to overall lower long-term healthcare costs.

PPI compliance and effect on healthcare costs

One paper included in the review addressed the issue of PPI compliance and effect on healthcare costs. Gosselin *et al* [25] found that patients compliant with PPI therapy had greater incremental healthcare cost savings compared with non-compliant patients (annual savings of $3261 *vs*. $2406) [25].

DISCUSSION

In this systematic review of economic evaluations of GERD medical management over the past decade, we identified eighteen articles meeting strict inclusion criteria for analysis. PPI therapy was preferred (*i.e.*, both more effective and less costly) as empiric therapy for patients with reflux symptoms, except in patient populations with high *H. pylori* prevalence, and this is reflected by clinical practice and guideline recommendations [28]. Although surgery is initially costly, many patients have good symptom control over time and thus surgery can be cost saving and cost-effective compared to medical therapy over time periods ranging from 3 years [15] to a lifetime [8]. Endoscopic anti-reflux procedures do not appear cost-effective compared to medical therapy based on available data from studies that examined what are now largely obsolete procedures. Should more innovative endoscopic GERD management strategies be introduced and adopted, more economic research will be needed to evaluate their relative cost-effectiveness.

As healthcare accounts for growing budgetary commitments worldwide, there has been an increased emphasis on evaluating therapies in terms of cost and quality. In turn, the research surrounding disease states often includes cost as a secondary outcome. Reporting of cost, however, is overly simplistic and does not necessarily imply value. Most of the articles that we initially identified were not included as they were simply cost-identification studies, and did not relate cost to actual benefit or effectiveness of therapy. Cost identification articles can be useful, as they may be used to design future economic evaluations. However, it is an important distinction that is often overlooked when reporting cost data and can lead to inappropriate conclusions about the relationship of cost to actual effectiveness of therapy.

In light of the increased emphasis on cost, it is critical that research reporting cost outcomes is evaluated rigorously. Recently, the ISPOR taskforce provided guidance for evaluating quality of economic evaluations with release of the CHEERs checklist. Overall, around 60% of the included articles met all CHEERs criteria. Those not meeting all of the CHEERs criteria mainly omitted method descriptions or disclosures of funding. As many cost studies involve sophisticated modeling techniques based on probability estimates and possible funding from pharmaceutical companies or device manufacturers, disclosure of funding sources is critical to ensure that readers can reliably assess any potential for bias. Investigators embarking on future research with cost outcomes should use the CHEERs checklist to guide study design and reporting of results. In turn, the criteria may help editors

and reviewers ensure consistent reporting and identification of bias in economic evaluation research.

Numerous medications can be taken for reflux symptoms including antacids, H_2RAs and PPIs. Economic evaluations comparing medical therapies found that PPI use is more effective than treatment with an H_2RA and less costly due to lower rates of symptom and esophagitis recurrence [20,23]. As there is very little evidence that any one PPI is superior in terms of efficacy, use of the cheapest PPI available dominated specific PPI therapeutic regimens [21]. The most recent Technical Review on GERD from the American Gastroenterological Association reflected the superiority of PPI therapy over H_2RAs [29] but did not specifically recommend one particular PPI formulation over others. A recent US population study using the National Ambulatory Medical Care Survey (NAMCS) found that both branded (esomeprazole) and generic (omeprazole) PPIs had significant increase in use from 2002–2009 [30]. There is very little evidence that more expensive PPIs offer additional major benefits over less costly PPIs for most GERD patients, especially for initial therapy. Therefore, practitioners in countries or settings without fixed formularies should be encouraged to use the least costly PPI formulation.

Numerous studies included in this review compared medical and surgical therapy for GERD. Laparoscopic surgery was found to meet cost-effectiveness thresholds, especially if time horizons were between 3 and 10 years [8,12–15], although was one study showed PPIs to dominate surgery (less costly and more effective) within 10 years [10]. This difference is probably due to the quality of life estimates (utilities) [27] that were essentially the same for both surgical and medical therapy based on two older studies [27,31]. The most recent study with impressive long term patient follow up (5 years) found that more patients randomized to early LNF (*vs.* medical therapy) had less frequent heartburn and regurgitation at 3 and 5 years follow up [8]. In addition, quality of life scores were greater in surgery patients at 5 years follow up [8]. Laparoscopic techniques to prevent acid reflux have very good long term outcomes in select patients [8,32,33] and non-laparoscopic anti-reflux surgery was the primary therapy for many patients with GERD prior to the introduction of PPIs [32]. However, surgery rates for GERD have declined over time. In 2005, there were 15,737 Nissen fundoplication procedures performed in the United States [34]. Although this is still one of the most common anti-reflux procedures, its use had declined by 27% from the late 1990s [34]. Patient and physician preferences have probably played a role in this trend towards less invasive (and mostly effective) medical treatment. However, the cost-effectiveness of surgery should not be underestimated, especially in patients with a definite diagnosis of GERD that is truly refractory to optimized medical treatment, perhaps because of volume reflux. Based on this review, there is little economic evidence that endoscopic anti-reflux procedures or performing endoscopy prior to PPI therapy are cost-effective strategies. Further research is also needed to determine if other emerging technologies for GERD, such as a magnetic device for lower esophageal sphincter augmentation [35], will be cost-effective, assuming safety and efficacy are demonstrated before widespread clinical adoption.

Limitations of this review include the inability to pool data due to the different time horizons and comparisons made in individual studies. Thus, it is difficult to obtain pooled estimates

of cost-effectiveness based on published data. Economic modeling is based on assumptions and probability estimates that usually require sensitivity analyses to test model integrity. The articles included in this review did report robust sensitivity analyses. However, limitations of economic evaluations include inability to account for treatment effects in different patient phenotypes. For instance, the definition for efficacy used in the clinical trials and modeling may vary considerably in studies of GERD (*e.g.*, global symptom scores [19], disease specific patient reported outcomes [8], health related quality of life [10], and symptom free days [21]). GERD is also a diagnosis that is sometimes given to patients as an explanation for a variety of upper gastrointestinal symptoms that, consequently, display a highly variable response to medical therapy. The models employed in the included literature assumed PPI prescribing is systematic and that patient compliance is substantial. In fact, in clinical practice, PPI prescriptions and subsequent PPI utilization have been found to be highly variable across settings [36–40]. The actual realized economic outcomes reported, especially regarding PPI therapy, are probably less than optimal in clinical practice.

In summary, this is the first systematic review of economic evaluations of GERD medical management. Any future evaluations should adhere to standard reporting measures so that readers can assess and compare quality of cost estimates and outcomes. Future economic evaluations of GERD medical management should also attempt to account for, and compare, different patient phenotypes and the large heterogeneity of treatment effects seen with anti-reflux therapy. In clinical practice, the primary focus should be on optimal care coordination of patients with reflux symptoms *via* cost-effective management strategies that are aligned with patient preferences [41].

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Abbreviations

GERD	gastroesophageal reflux disease
PPI	proton pump inhibitor
US	United States
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
NHS	National Health Service
ICER	incremental cost-effectiveness ratio
LNF	laparoscopic Nissen fundoplication
QALY	quality adjusted life year
QALM	quality adjusted life month

H_2RA	Histamine-2 Receptor Antagonist
NAMCS	National Ambulatory Medical Care Survey
NICE	National Institute for Heath and Care Excellence
UK	United Kingdom
ACA	Patient Protection and Affordable Care Act
PCORI	Patient Centered Outcomes Research Institute

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41. AHRQ Executive Summary. Effective Health Care Program Management Strategies for Gastroesophageal Reflux Disease : An Update.

Key points for decision makers

- Gastroesophageal reflux disease (GERD) is one of the most costly digestive diseases worldwide yet very few published studies fulfill quality criteria as full economic evaluations.
- Empiric proton pump inhibitor therapy for reflux symptoms appears to be the most cost effective strategy (*vs*. diagnostic endoscopy or *H. pylori* testing) for initial GERD medical management. However, practitioners should be encouraged to use the least costly formulation as effectiveness is similar across formulations.
- Future economic evaluations of GERD medical management should attempt to account for, and compare, the large heterogeneity of patient phenotypes and treatment effects seen with anti-reflux therapy.

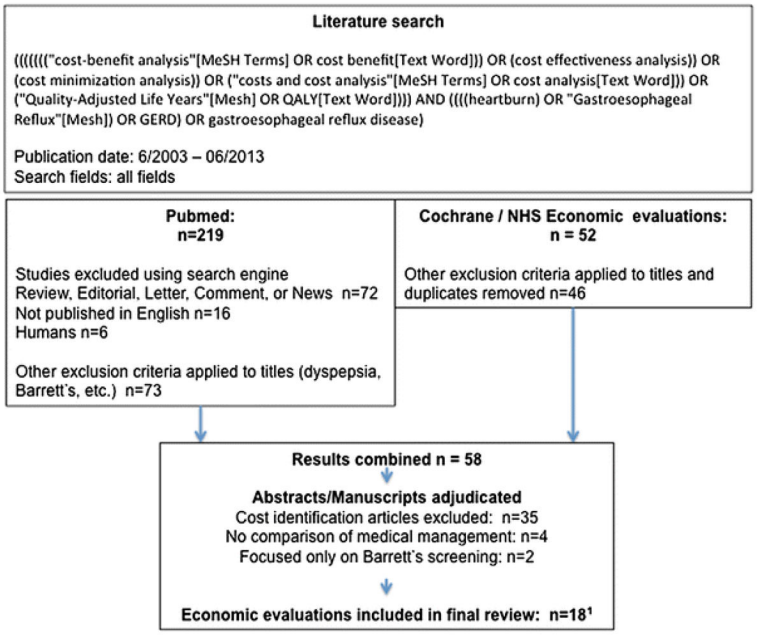

Figure 1. Review search strategy and results

[1]One additional article was included via expert opinion on manuscript review that was not identified via the literature search

Table 1

General characteristics of included studies

Study characteristic	n (%) (T otal n=18)	References
Study design		
Markov model	9 (50%)	[9, 10, 12–14, 17, 20, 21, 23]
Randomized trial	5 (28%)	[8, 11, 15, 16, 19]
Decision analysis	3 (17%)	[18, 22, 24]
Retrospective	1 (5%)	[25]
Comparisons[1]		
PPIs vs. surgery	7 (39%)	[8, 10–15]
Different PPI regimens	7 (39%)	[16–21, 23]
PPIs vs. endoscopic management strategies (diagnosis and therapy)	4 (22%)	[9, 17, 22, 24]
PPIs vs. H_2RAs	2 (11%)	[20, 23]
Cost outcome perspective		
Public Healthcare system	15 (83%)	[8–17, 19–23]
Societal	1 (6%)	[24]
3rd party payer (Private Insurance)	1 (6%)	[25]
Employer	1 (6%)	[18]
Time horizon		
≤ 1 year	8 (45%)	[11, 17–21, 23, 24]
> 1 to ≤ 10 years	6 (33%)	[9, 10, 12, 15, 16, 22]
> 10 years to lifetime	4 (22%)	[8, 13, 14, 25]
Outcome currency reported		
US dollars ($)	7 (39%)	[10, 12, 17, 18, 20, 22, 25]
British pounds (£)	5 (28%)	[8, 11, 13, 14, 21]
Canadian dollars ($)	3 (17%)	[9, 15, 19]
Euros (€)	2 (11%)	[16, 24]
Japanese Yen (¥)	1 (5%)	[23]

[1] Proportion > 100% due to multiple comparisons made in individual studies

Table 2

Quality of the economic evaluations as assessed by CHEERS guidelines

	n (%) (Total n=18)	References
Articles reporting 100% of CHEERS checklist items	11 (61%)	8–15, 18–19, 21
Missing Items		
Title: Economic evaluation description	1 (5%)	16
Methods: No mention of discount rate	4 (22%)	16, 23–25
Results: Missing reporting of study parameters	2 (11%)	16, 25
Methods: Missing description of sampling uncertainty	1 (5%)	24
Other: Missing source of funding	3 (17%)	22–24
Other: Missing conflicts of interest disclosure	4 (22%)	17, 20, 22–24

Table 3

Summary table of economic evaluation outcomes

First Author, Year, Ref	Study Design	Population / Base case	Comparison	Perspective	Cost outcome	Results
Grant, 2013, [8]	Randomized trial, 5yr follow up	Chronic GERD	Laparoscopic surgery vs. continued medical management	UK NHS	ICER (£)	Surgery £7028 per additional QALY vs. medical management
Goeree, 2011, [15]	Randomized trial	Chronic GERD	LNF vs. PPIs	Canadian Health System	ICER ($Can)	LNF $29,404/QALY vs. PPIs
Moayyedi, 2010, [19]	Randomized intervention	GERD diagnosis	PPI symptom test based management strategy vs. controls	Canadian Health System	ICER ($Can)	$763 / QALM gained
Gosselin, 2009, [25]	Retrospective cohort	GERD diagnosis	Compliant vs. non-compliant PPI users	Third-party payers (US)	Incremental healthcare costs ($US)	Compliant: decline of $3261 vs. Non-compliant: decline of $2406 per patient year
Epstein, 2009, [12]	Markov model	45 y/o male GERD patients stable on medication	Laparoscopic surgery vs. continued PPIs	UK NHS	ICER ($US)	$4385 / QALY
Grant, 2008, [13]	Markov model	45 y/o male GERD patients stable on medication	Laparoscopic surgery vs. continued PPIs	UK NHS	ICER (£)	£19,288/QALY
Comay, 2008, [9]	Markov model	GERD patients partially responsive to PPIs	PPI daily vs. LNF vs. Stretta endoscopic procedure	Canadian Health System	ICER ($Can)	Stretta $352,000/QALY vs. PPIs LNF $392,432/QALY vs. PPIs
Giannini, 2008, [16]	Randomized trial	Patients with ≥3 months of reflux symptoms	Empiric esomeprazole 40mg daily vs. endoscopy oriented treatment strategy	Italian Health Service	Cost per treated patient (€)	Empirical €88.34 vs. Endoscopy €127.06
Doan, 2008, [18]	Decision analysis	100,000 patients w/20% GERD prevalence	Continuous PPI therapy vs. no treatment	US Employers	Savings per treated patient per year ($US)	Treatment saved $1630 per patient per year
Bojke, 2007, [14]	Markov model	45 y/o GERD patients	Long term PPI vs. immediate laparoscopic surgery	UK NHS	ICER (£)	£180 / QALY
Baldi, 2006, [24]	Decision analysis	Patients with unexplained chronic cough	6 diagnostic strategies (including empiric PPI treatment)	Societal	Mean cost (€) (equivalent effectiveness)	PPI empiric treatment had lowest cost (€211)
You, 2006, [17]	Markov model	Patients with weekly attacks of heartburn	Empiric PPI vs. H. pylori test/treat vs. Endoscopic diagnosis vs. No therapy	Public Health Provider, Hong Kong	Incremental cost per ulcer treated ($US)	PPI $2158 vs. H Pylori test/ treat $1778 vs. Endoscopy $1797 vs vs. No therapy

First Author, Year, Ref	Study Design	Population / Base case	Comparison	Perspective	Cost outcome	Results
Habu, 2005, [23]	Markov model	Patients with endoscopically confirmed reflux esophagitis	PPI first vs. H2RA first then PPI step up	Japanese Health Insurance System	ICER (¥ yen) (healed esophagitis)	PPI ¥211/day without esophagitis vs. H2RA ¥217/day without esophagitis
Remak, 2005, [21]	Markov model	GERD diagnosis	7 PPIs (acute and long term treatment, on demand vs. continuous vs. no treatment)	UK NHS	ICER (£)	**1** Omeprazole dominated all strategies. **2** Rabeprazole was cost effective at £3.42 per symptom free day
Cookson, 2005, [11]	Randomized trial	Patients with GERD and on PPI ≥3 mo	PPI maintenance vs. LNF	UK NHS	ICER (£)	LNF £5515 vs. PPIs (for physiological normal acid score at 3 mo)
Arguedas, 2004, [10]	Markov model	45 y/o with esophagitis secondary to GERD	PPI vs. LNF	US Medicare	ICER ($US)	PPI therapy dominated LNF
Harewood, 2003, [22]	Decision analysis	Patients w/ GERD responsive to PPI QD or BID	Endoluminal plication vs. radiofrequecny coagulations vs. PPI	US Medicare	Cost minimization ($US)	PPI therapy least costly regardless of time if < $140 / month or endotherapy > $3400
You, 2003, [20]	Markov model	Patients with healed esophagitis	H2RA vs. low dose PPI vs. standard dose PI	Public Health Provider, Hong Kong	ICER ($US)	$905 standard dose PPI vs. $1374 low dose PPI vs. $1633 H2RA / QALY gained