

Systematic review: direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease

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SUMMARY

Background: Five proton pump inhibitors are now available for use in North America. Claims of differences in the clinical efficacy of different strengths and/or agents have been made.

Aim: To identify any consistent evidence of differences in outcomes between agents or doses within this class of drugs.

Methods: A search of the medical literature was performed in two electronic databases, and randomized controlled trials of higher quality were included in the assessment.

Results and conclusions: Thirty-two trials met our criteria. No convincing data were found to indicate that low doses of proton pump inhibitors are as effective as

standard doses of proton pump inhibitors in the healing of erosive oesophagitis or in the relief of symptoms of gastro-oesophageal reflux disease; however, they may be as effective as maintenance therapy for gastro-oesophageal reflux disease and peptic ulcer disease. Differences were found between the standard doses of proton pump inhibitors with regard to the onset of symptom relief in gastro-oesophageal reflux disease (lansoprazole was faster than omeprazole, and esomeprazole was faster than both lansoprazole and omeprazole) and the healing of oesophagitis (esomeprazole was superior to both omeprazole and lansoprazole). Despite these differences, there are as yet insufficient data to establish the superiority of any one agent over all others across all disease states treated with these agents.

INTRODUCTION

Five proton pump inhibitors are now available in North America for the treatment of acid-related disorders (omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole). Pantoprazole is available in only one dose strength, whereas two dosages (standard and half dose) exist for the other four agents. Although the lower dose of a proton pump inhibitor may cost less

than the standard dose in some countries, including Canada and the UK, there are conflicting data on the clinical effectiveness of the lower dose of the proton pump inhibitors in the management of acid-related diseases.

In addition, each of the five commercially available proton pump inhibitors has unique pharmacokinetic properties and pharmacodynamic activity, but the results are variable.¹ However, these pharmacological differences are relevant only if they equate to clinically important differences in efficacy, tolerability or safety of the compounds. Despite the widespread marketing of these compounds as having potential differences in

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therapeutic efficacy, there have been few head-to-head trials measuring clinically meaningful outcomes. This has led some to compare the clinical outcomes of individual proton pump inhibitors across separate trials. This form of comparison is inappropriate because overt and/or covert differences in study design and population may bias the outcomes. Thus, only head-to-head studies are appropriate for determining whether clinical differences exist.

We hypothesized that there would be important differences when the efficacy of half-dose proton pump inhibitor is compared with that of standard-dose proton pump inhibitor, or when the standard doses of these agents are compared against each other. The specific aims of this study were to: (i) perform a systematic review of the English literature for articles of high methodological quality that compared proton pump inhibitors with each other and/or low, standard and/or high doses of a specific proton pump inhibitor for the initial treatment and/or maintenance of gastro-oesophageal reflux disease (GERD); (ii) perform a systematic review of the English literature for articles of high methodological quality that compared proton pump inhibitors with each other and/or low, standard and high doses of a specific proton pump inhibitor in the treatment and/or maintenance of remission of peptic ulcer disease; (iii) identify any reproducible and consistent differences in outcomes between agents or doses within this class of drugs, the quality of the evidence and, if such differences existed, establish a clinical recommendation on the use of proton pump inhibitors that would optimize clinical outcomes; we also sought to determine whether the evidence supported a specific recommendation regarding best practice in the use of proton pump inhibitors; (iv) identify areas of unmet needs in the clinical use of proton pump inhibitors to direct future research.

METHODS

Search strategy

A search of the on-line bibliographic databases MEDLINE and PUBMED was independently performed by the two authors to identify articles published between 1988 and 2002, using the terms proton pump inhibitor, lansoprazole, esomeprazole, rabeprazole, omeprazole, pantoprazole, peptic ulcer disease (PUD) and gastro-oesophageal reflux disease (GERD). Bibliographies from

all potentially relevant articles were also manually searched. Studies were selected if they met the following criteria:

- (a) Randomized controlled trial directly comparing two or more specific proton pump inhibitors or doses.
- (b) Prospective evaluation of a measurable relevant clinical end-point (healing of oesophagitis, healing of duodenal or gastric ulcer or symptom resolution).
- (c) Complete reporting of the frequency of detection of other diseases and outcomes in studies of proton pump inhibitor use in functional dyspepsia in the event that patients with GERD or ulcer disease were included in these studies.
- (d) Trial published in full manuscript form in the English language.

Study quality assessment

Study quality was assessed using the Jadad scale, an accepted and specific scale for assessing the quality of the design of randomized controlled trials (Table 1).² A priori, it was decided to include only articles with a Jadad scale of three or above in the final analysis and, furthermore, those with scores of four or five were classified as being of 'high quality'. Studies with Jadad scales of two or less were initially reviewed, but were not included in the final analysis. Data pre-determined to be relevant to this analysis were abstracted on to a standardized form. Differences between investigators with regard to the inclusion of articles, data abstracted and methodological score were resolved by a telephone adjudication conference with both authors agreeing on the final article inclusion, data and score.

Table 1. Jadad scoring system²

Randomization	
2 points	Describes method of randomization and includes appropriate method
1 point	States randomized but no description of method
Blinding	
2 points	Double blind with method described
1 point	States blind but no description of method
Withdrawals/dropouts	
1 point	Describes number of withdrawals and reasons

Adapted from Jadad *et al*.²

Data extraction

Following abstraction of the data, a spreadsheet was constructed and analysed with regard to the outcomes of the various comparisons between the proton pump inhibitors (GERD and ulcer healing or symptom relief studies, GERD and ulcer maintenance studies, quality scores of the studies, etc.) that had been pre-determined to be of clinical importance.

Quality of the evidence

Studies of high-quality design and with clinically relevant end-points that directly compared the efficacy of two or more proton pump inhibitors or doses of proton pump inhibitors in parallel were sufficient to determine whether meaningful clinical differences in outcomes occurred within the proton pump inhibitor class or dose range. These studies ideally should follow evidence-based methodology, i.e. should be randomized using concealed allocation techniques, should be double-blind, should be analysed by an intention-to-treat method, should have complete accounting of all patients entered into the trial and should be of a sufficient size in order to minimize bias and to ensure that the results

obtained are reliable and valid. Only when trials exhibiting this 'Level I' quality study design (Table 2)³ consistently (i.e. two or more trials) demonstrated the superiority of outcome of an agent within a class, without the presence of conflicting studies in the literature, could a 'Grade A' recommendation be made (the only grade of recommendation for which a treatment can be reliably recommended as being superior) (Table 3).³⁻⁵ As such, the quality of evidence for a particular focused clinical question was then assigned a 'grade' following systematic assessment of the data using this previously described grading method.

RESULTS

Using the above search strategy, 3624 citations on proton pump inhibitors as a general term were identified, with 1100 on lansoprazole, 5734 on omeprazole, 222 on rabeprazole, 406 on pantoprazole and 2914 on esomeprazole identified by search of the specific compounds. Further review of these results identified the following randomized controlled trials: 276 on proton pump inhibitors as a general term, 274 regarding lansoprazole, 1092 regarding omeprazole, 222 regarding rabeprazole, 406 regarding pantoprazole and 1065

Table 2. Levels of evidence (only Level I and II evidence should be used to make clinical recommendations)

Level	Evidence
I	Evidence from randomized controlled trials with low false positive rates (i.e. significant <i>P</i> values), adequate sample sizes (low likelihood of type II errors) and appropriate methodology (low likelihood of type I errors)
II	Evidence from randomized controlled trials with high false positive rates, inadequate sample sizes or inappropriate methodology
III	Evidence from non-randomized trials using a contemporaneous cohort of controls
IV	Evidence from non-randomized trials using a historical cohort of controls
V	Evidence from case series without controls

Adapted from Cook *et al.*³

Table 3. Graded recommendations for clinical practice

Grade	Strength of evidence to guide clinical practice
A	Supported by two or more Level I studies without conflicting evidence from other Level I studies
B	Supported by two or more Level I studies with conflicting evidence from other Level I studies OR supported by only one Level I or two or more Level II studies
C	Supported by Level III-V evidence

Adapted from Guyatt *et al.*⁴ *Users Guides to the Medical Literature*⁵ and Cook *et al.*³

Table 4. Lansoprazole vs. other proton pump inhibitors

Clinical end-point	Level of evidence/Jadad score	Grade	Reference
Healing (%) and symptom relief (%) in GERD			
In healing of oesophagitis, LAN 30 mg (84.8%) demonstrated similar efficacy to OME 20 mg (86.5%) at 8 weeks	One Level I study, Jadad score of 4	B	19
In healing of oesophagitis, LAN 30 mg (86%) demonstrated similar efficacy to PAN 40 mg (90%) at 8 weeks	One Level I study, Jadad score of 4	B	10
In healing of oesophagitis, LAN 30 mg (87.5%) demonstrated similar efficacy to OME 40 mg (80.6%) at 4 weeks	One Level II study, Jadad score of 4	B	9
In GERD symptom relief in patients with oesophagitis, LAN 30 mg (56%) was superior to OME 20 mg (49%) on days 1–3 of this 8-week study ($P < 0.0001$)	One Level I study, Jadad score of 4	B	16
In relief of heartburn and epigastric pain, LAN 15 mg (53%) was superior to OME 10 mg (41%) at 2 weeks ($P = 0.007$)	One Level I study, Jadad score of 4	B	22
In healing of oesophagitis, OME 20 mg (87%) and LAN 30 mg (87%) were superior to LAN 15 mg (75%) at 8 weeks ($P < 0.05$)	One Level I study, Jadad score of 4	B	24
Maintenance of healing in GERD (%)			
In prevention of relapse in patients with oesophagitis and stricture, OME 20 mg b.d. (90%) was superior to LAN 30 mg b.d. (20%) and PAN 40 mg b.d. (30%) at 4 weeks ($P < 0.01$)	One Level II study, Jadad score of 3	B	21
In maintenance of healing of oesophagitis, LAN 30 mg (90.5%) demonstrated similar efficacy to OME 20 mg (91%) at 48 weeks	One Level I study, Jadad score of 4	B	26
In maintenance of healing of oesophagitis, daily LAN 15 mg (82%) demonstrated similar efficacy to alternate-day therapy with LAN 30 mg (77%) at 6 months	One Level I study, Jadad score of 5	B	30
Healing (%) and maintenance of healing (%) of ulcers			
In two studies of healing of duodenal ulcer, LAN 30 mg (93.9% and 97.7%) demonstrated similar efficacy to OME 20 mg (97.5% and 96.7%) at 4 weeks and similar efficacy in maintenance of ulcer healing over 18 months	One Level I study, Jadad score of 4 Two Level II studies, Jadad score of 3–4	A	39, 40
In maintenance of healing of duodenal ulcers, LAN 30 mg (85%) demonstrated similar efficacy to LAN 15 mg (70%) at 12 months	One Level II study, Jadad score of 4	B	37

GERD, gastro-oesophageal reflux disease; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole.

regarding esomeprazole. The sub-classes of randomized controlled trials in the English language were as follows: omeprazole and GERD, 104 trials; omeprazole and ulcer disease, 726 trials; lansoprazole and GERD, 24 trials; lansoprazole and ulcer disease, 193 trials; rabeprazole and GERD, 10 trials; rabeprazole and ulcer disease, 34 trials; pantoprazole and GERD, 11 trials; pantoprazole and ulcer disease, 70 trials; esomeprazole and GERD, 110 trials; esomeprazole and ulcer disease, 496 trials. Of these numerous studies, 36 met our a priori criteria for analysis and/or were relevant to our specific aims and were abstracted.^{6–41} On further detailed evaluation during the abstraction process, one of these studies was found to have been carried out without blinding and was excluded,¹² two were found to have a Jadad score of only two and were excluded from further analysis^{13, 29} and one study's primary outcome was based on

surrogate end-points (intra-oesophageal pH) and was also excluded.¹⁸ The findings from the systematic review of the remaining 32 studies are summarized and presented in Tables 4–8. The focused clinical questions that had been formulated prior to the search were then addressed using these data.

Focused clinical question 1: are lower doses of proton pump inhibitors similar to standard doses in clinical efficacy?

Low doses of proton pump inhibitors were not as effective as standard doses of proton pump inhibitors in the healing of erosive oesophagitis or in the treatment of GERD symptoms.^{24, 25} Some data suggested that low-dose proton pump inhibitors had a similar efficacy to standard doses in the maintenance treatment of GERD and ulcer disease.^{31–33, 37}

Table 5. Pantoprazole vs. other proton pump inhibitors

Clinical end-point	Level of evidence/Jadad score	Grade	Reference
Healing (%) and symptom relief (%) in GERD			
In healing of oesophagitis, PAN 40 mg (74% and 90%) demonstrated similar efficacy to OME 20 mg (78% and 94%) at 4 and 8 weeks	One Level I study, Jadad score of 4	B	23
In GERD symptom relief, OME 20 mg (84% and 87%) demonstrated similar efficacy to PAN 40 mg (84% and 89%) and LAN 30 mg (78% and 81%) at 4 and 8 weeks	One Level II study, Jadad score of 4	B	8
Healing (%) and maintenance of healing (%) of ulcers			
In two studies of healing of duodenal and gastric ulcer, PAN 40 mg (96% and 78.5%) demonstrated similar efficacy to OME 20 mg (91% and 70%) at 4 weeks	Two Level I studies, Jadad score of 4	A	36, 38

GERD, gastro-oesophageal reflux disease; LAN, lansoprazole; OME, omeprazole; PAN, pantoprazole.

Table 6. Rabeprazole vs. other proton pump inhibitors

Clinical end-point	Level of evidence/Jadad score	Grade	Reference
Healing (%) and symptom relief (%) in GERD			
In two studies of healing of oesophagitis, RAB 20 mg (91% and 92%) demonstrated similar efficacy to OME 20 mg (94% and 94%) at 8 weeks	Two Level II studies, Jadad score of 3 and 5	B	6, 7
In GERD symptom relief, RAB 20 mg (83.9%) demonstrated similar efficacy to OME 40 mg (82.8%) on day 4 of treatment	One Level II study, Jadad score of 4	B	17
Maintenance of healing (%) of GERD			
In the maintenance of healing of oesophagitis, RAB 10 mg (95%) and RAB 20 mg (96%) demonstrated similar efficacy to OME 20 mg (95%) at 52 weeks	One Level I study, Jadad score of 4	B	31
Healing (%) and maintenance of healing (%) of ulcers			
In two studies of healing of ulcer, RAB 20 mg (98% duodenal ulcer and 91% gastric ulcer) demonstrated similar efficacy to OME 20 mg (93% duodenal ulcer and 91% gastric ulcer) at 4 weeks for duodenal ulcer and 6 weeks for gastric ulcer	Two Level I studies, Jadad score of 4	A	34, 35

GERD, gastro-oesophageal reflux disease; OME, omeprazole; RAB, rabeprazole.

Focused clinical question 2: is any proton pump inhibitor superior to another in clinical efficacy using standard doses of these agents?

Table 4 summarizes the comparison of efficacy of lansoprazole vs. the other proton pump inhibitors. A single study demonstrated similar healing rates of oesophagitis with lansoprazole 30 mg vs. omeprazole 20 mg.¹⁹ Similarly, another study demonstrated similar rates of healing of oesophagitis between pantoprazole 40 mg and lansoprazole 30 mg.¹⁰ There was also a single study demonstrating that esomeprazole 40 mg was superior to lansoprazole 30 mg in the healing of erosive oesophagitis, and another demonstrating the superiority of low-dose esomeprazole vs. low-dose

lansoprazole in the maintenance of healing^{15, 27} (Table 7). One study compared oesophagitis healing and symptom relief with low-dose lansoprazole vs. standard-dose proton pump inhibitor and found the low dose to be less effective.²⁴ Standard-dose lansoprazole was more effective than standard-dose omeprazole in GERD symptom relief in the first week of study.¹⁶ Low-dose lansoprazole was more effective than low-dose omeprazole in relieving heartburn symptoms in the first 2 weeks of study in another trial.²²

Table 5 summarizes the comparison of efficacy of pantoprazole vs. the other proton pump inhibitors. Healing rates of oesophagitis and peptic ulcer were similar for standard-dose pantoprazole and omeprazole.^{23, 36, 38}

Table 7. Esomeprazole vs. other proton pump inhibitors

Clinical end-point	Level of evidence/Jadad score	Grade	Reference
Healing (%) and symptom relief (%) in GERD			
In healing of oesophagitis and GERD symptom relief, ESO 40 mg (92.6%) was more efficacious than LAN 30 mg (88.8%) at 8 weeks ($P = 0.0001$)	One Level I study; Jadad score of 5	B	15
In two studies of healing of oesophagitis and GERD symptom relief, ESO 40 mg (94.1% and 93.7%) was more efficacious than OME 20 mg (86.9% and 84.2%) at 8 weeks ($P < 0.05$ and $P < 0.001$, respectively)	Two Level I studies; Jadad score of 5	A	11, 14
Maintenance of healing (%) of GERD			
In maintenance of remission of oesophagitis, ESO 20 mg (83%) was more effective than LAN 15 mg (74%) at 6 months ($P < 0.0001$)	One Level I study, Jadad score of 5	B	27
In two studies of the maintenance of healing of erosive oesophagitis, ESO 40 mg (94% and 88%) demonstrated similar efficacy to ESO 20 mg (93% and 79%) at 6 months	Two Level I studies, Jadad score of 4	A	32, 33

GERD, gastro-oesophageal reflux disease; ESO, esomeprazole; LAN, lansoprazole; OME, omeprazole.

Table 8. Low- and high-dose omeprazole comparisons

Clinical end-point	Level of evidence/Jadad score	Grade	Reference
Healing (%) and symptom relief (%) in GERD			
In symptom relief of GERD in those without oesophagitis, OME 10 mg (35%) demonstrated similar efficacy to OME 20 mg (41%) at 4 weeks	One Level II study, Jadad score of 3	B	20
In symptom relief of GERD, OME 20 mg (61%) was superior to OME 10 mg (49%) at 4 weeks ($P < 0.02$)	One Level I study, Jadad score of 4	B	25
In healing and GERD symptom relief in patients with oesophagitis, OME 20 mg (73.5%) demonstrated similar efficacy to OME 40 mg (74.7%) at 8 weeks	One Level II study, Jadad score of 4	B	28
Ulcer healing (%)			
In healing of gastric ulcer, OME 40 mg (56% and 83%) was superior to OME 20 mg (48% and 75%) at both 4 and 8 weeks ($P < 0.01$ and $P < 0.05$, respectively)	One Level I study, Jadad score of 3	B	41

GERD, gastro-oesophageal reflux disease; OME, omeprazole.

Table 6 summarizes the comparison of efficacy of rabeprazole vs. the other proton pump inhibitors. In two studies measuring the healing of oesophagitis, rabeprazole 20 mg was similar to omeprazole 20 mg.^{6, 7} There were no data comparing oesophagitis healing and/or GERD symptom relief with lower doses of rabeprazole vs. standard doses of any proton pump inhibitor. A single study indicated that low-dose rabeprazole (10 mg) was similar to standard-dose rabeprazole (20 mg) and standard-dose omeprazole (20 mg) in the maintenance of healing of oesophagitis.³¹ Two studies demonstrated that peptic ulcer healing rates with rabeprazole (20 mg) and omeprazole (20 mg) were similar.^{34, 35}

Table 7 summarizes the comparison of efficacy of esomeprazole vs. the other proton pump inhibitors. Two

studies demonstrated the superiority of esomeprazole 40 mg over omeprazole 20 mg in the healing of oesophagitis and time to sustained heartburn relief.^{11, 14} One study demonstrated the superiority of esomeprazole 40 mg vs. lansoprazole 30 mg in the healing of oesophagitis and time to sustained heartburn relief.¹⁵ One trial demonstrated that low-dose esomeprazole (20 mg) was superior to low-dose lansoprazole (15 mg) in the maintenance of healing of oesophagitis.²⁷ Low-dose esomeprazole was as effective in the maintenance of oesophagitis healing as standard-dose esomeprazole.^{32, 33} There were no data comparing oesophagitis healing and/or GERD symptom relief with lower doses of esomeprazole vs. standard doses of any proton pump inhibitor.

Table 8 summarizes the comparison of efficacy of omeprazole vs. other proton pump inhibitors not

covered in Tables 4–7. One study demonstrated no difference in oesophagitis healing or symptom relief between standard- and high-dose omeprazole.²⁸ Two studies evaluated low- vs. standard-dose omeprazole for GERD symptom relief, with one showing similar efficacy and the other inferior efficacy.^{20, 25} In the healing of large gastric ulcers, high-dose omeprazole was superior to standard-dose omeprazole.⁴¹

DISCUSSION

This systematic review demonstrates that studies comparing the clinical outcomes of proton pump inhibitors and/or their various doses vary widely in quality, with the vast majority being of low methodological quality and not meeting our criteria for inclusion. The criteria employed to select studies for this systematic review have been widely used and are designed to facilitate a reliable evaluation of the evidence and the rigor with which it was collected.⁴² As with all investigations, our study has some limitations. We did not evaluate studies that were published in languages other than English, and we did not evaluate studies that had not been published as full manuscripts; thus abstracts, unpublished trials or papers published in journals not referenced in MEDLINE were not analysed. The exclusion of these studies may have led to bias in the results of this analysis. The strengths of our review are that we used explicit criteria to evaluate the studies and these criteria were determined a priori. We also performed an exhaustive search of the literature and analysed the evidence using well-established evidence-based medicine criteria.

We attempted to address two clinically relevant questions with our analysis. One important question was whether any one proton pump inhibitor is superior to another using standard doses of these compounds. When the healing of oesophagitis was considered, two high-quality studies showed that esomeprazole 40 mg was superior to omeprazole 20 mg, and another showed that esomeprazole 40 mg was superior to lansoprazole 30 mg.^{11, 14, 15} The therapeutic gain ranged from 4 to 10% in these three studies, and a *post hoc* analysis of the data from two of the studies indicated that this therapeutic gain was likely to be related to the superior healing rates in GERD patients with more severe grades of oesophagitis (i.e. Los Angeles Grades C and D). In addition, with regard to the maintenance of healing of oesophagitis, a single study of high quality

showed better maintenance of healing with low-dose esomeprazole compared with low-dose lansoprazole.²⁷ These data indicate that esomeprazole is superior to all proton pump inhibitors with which it has been compared in terms of the healing of oesophagitis. One possible explanation for these differences in clinical efficacy is related to differences in pharmacokinetics and pharmacodynamics between the compounds. Whether these differences in pharmacology account for some or all of the differences in efficacy is unknown. In addition, whether esomeprazole is also superior to the other two proton pump inhibitors (pantoprazole and rabeprazole) in the healing of oesophagitis, symptom relief or maintenance of healing has not been tested, and esomeprazole's superiority over lansoprazole in the healing of oesophagitis has not been substantiated by a second high-quality trial. No other trial in the literature comparing the healing rates of oesophagitis between any other proton pump inhibitors has demonstrated any consistent differences in healing between any of these other agents. The clinical relevance of the differences in healing rates between esomeprazole and omeprazole or lansoprazole is beyond the scope of this review but, by necessity, should also include considerations of cost and patient preference. When GERD symptoms alone are considered, two studies have demonstrated that lansoprazole is superior to omeprazole in symptom relief as a secondary end-point in the first few weeks after therapy is initiated, with symptom relief at later time points being similar between these two agents.^{16, 22} As a secondary end-point, esomeprazole was faster than either omeprazole or lansoprazole in sustained heartburn resolution in the three studies evaluating this.^{11, 14, 15} No firm conclusions can be made with regard to GERD symptom relief with the proton pump inhibitors, other than the observations described above in the first 1–2 weeks of treatment, as almost all studies show similar outcomes in symptom relief over longer periods of observation, and no study has evaluated the speed of symptom relief between proton pump inhibitors as a primary outcome measure.

What about the clinical use of lower doses of proton pump inhibitors? There are few substantive data indicating that low doses of proton pump inhibitors are as effective as standard doses of proton pump inhibitors in the management of acid-related diseases. The data that do exist indicate that low doses of proton pump inhibitors are inferior to standard doses of proton pump inhibitors in the healing of oesophagitis and

GERD symptom relief.^{24, 25} Other data indicate that low-dose proton pump inhibitors may be therapeutically similar to standard-dose proton pump inhibitors in the maintenance of GERD or peptic ulcer disease.^{31–33, 37} These differences in findings in the trials investigating clinical outcomes with low-dose proton pump inhibitors are in part probably related to sub-optimal study design. In general, studies comparing low doses and standard doses of proton pump inhibitors have been powered to detect only relatively large effect size differences, indicating that smaller but clinically meaningful outcomes may not have been detected. As there are no data to indicate the equal efficacy of lower dose proton pump inhibitors in healing and symptom relief in patients with GERD, the use of low doses of proton pump inhibitors for this indication cannot be recommended at this time. However, the maintenance of the healing of oesophagitis and peptic ulcers has been demonstrated to be similar with both low- and standard-dose proton pump inhibitors, and low-dose proton pump inhibitor use can be recommended for this indication, although the data supporting this use are few.

When taken as a whole, the data support the following clinical recommendations, not taking into account cost and other factors that affect clinical decisions on drug use. For the healing of oesophagitis, esomeprazole is the only proton pump inhibitor that has been demonstrated to show superior healing in head-to-head studies with other proton pump inhibitors (Grade A recommendation). For GERD symptom relief, all five proton pump inhibitors demonstrate similar efficacy after 1–2 weeks, but lansoprazole and esomeprazole are the only agents to demonstrate a hastening of the speed of symptom relief in head-to-head studies with other proton pump inhibitors (Grade A). Low-dose proton pump inhibitors are not as effective as standard-dose proton pump inhibitors for the healing of oesophagitis and symptom relief (Grade B). Peptic ulcer healing is similar when using standard doses of any proton pump inhibitor (Grade A). No single proton pump inhibitor or dose has been studied head to head with all other agents within the class and for all clinical indications. As such, no agent or dose can be recommended as being superior for all indications for which proton pump inhibitors are used based on the currently available data.

Our analysis suggests several clinical areas that require further study with regard to the use of proton pump inhibitors. The data suggest that low-dose proton pump inhibitors are less effective than standard-dose

proton pump inhibitors in the healing of erosive oesophagitis and in the elimination of GERD symptoms, but the evidence supporting this conclusion is sub-optimal and requires further study. These studies will need to be adequately powered to detect modest differences in efficacy in order to fully address this issue. Few head-to-head, high-quality studies have compared the effect of the different proton pump inhibitors on meaningful clinical outcomes. Further studies are warranted to determine whether an agent (or agents) within this class is superior to one or more other agents within the class for diseases for which these agents are in common use. No high-quality studies have compared the efficacy of individual proton pump inhibitors or their different doses beyond 6 months, and few comparative studies have compared agents even for 8 weeks. More head-to-head healing and symptom relief studies are needed, as well as longer term efficacy studies, in order to generate data that will determine whether there are differences in efficacy between the proton pump inhibitors. An additional area that needs to be addressed as newer agents of this class (which provide even more intensive acid suppression) are introduced is whether safety concerns or unwanted long-term side-effects, which until now have not been noted with the existing five proton pump inhibitors, will become an important determinant in selecting a proton pump inhibitor for clinical use.

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