H2-antagonists versus proton pump inhibitors for gastro-esophageal reflux in adults

QUESTION
Should adults with gastro-esophageal reflux be treated with H2-antagonists compared to proton pump inhibitors?

CONTEXT	Gastro-esophageal reflux disease
Gastro-oesophageal reflux disease (GORD) appears as a reflux of gastroduodenal contents into the oesophagus that interferes in patient's quality of life with symptoms of heartburn or regurgitation. Up to 25% of people have symptoms of GORD, but only one quarter of patients have oesophagitis visible through endoscopy. Risk factors for GORD are not well established, but some data that factors such as obesity, smoking or alcohol increases its risk. The most validated methods to classify GORD severity are Los Angeles classification and the Savary-Miller classification. Treatment aims to relieve reflux symptoms, increase healing rates, and reduce GORD related complications.	

INTERVENTION	H2-anagonists versus proton pump inhibitors
Symptoms relieving (initial treatment) Proton pump inhibitors are more effective than H2 receptor antagonists to decrease the rate of people with persistent oesophagitis at 4 and 12 weeks. *Moderate quality evidence.*	
Relapse of reflux symptoms (maintenance treatment of GORD) Proton pump inhibitors are more effective at 6–12 months to decrease the rate of patients that relapse of oesophagitis or relapse of reflux symptoms in those patients that healed oesophagitis. *Moderate quality evidence.*	
Adverse effects Proton pump inhibitors and H2 receptor antagonists showed similar rates of adverse effects. *Moderate quality evidence.*	

Summary of the Evidence	
Benefits	A Clinical Evidence review (search date 2007) [1] found one Cochrane review (search date 2004; 34 RCTs; 5887 patients) that compared proton pump inhibitors (PPIs) versus H2 receptor antagonists (H2RAs) or H2RAs added to prokinetics [2]. At 4 and 12 weeks, the results showed that PPIs significantly decreased the rate of persistent oesophagitis compared with H2RA in the initial treatment (at 4w; 26 RCTs, 4032 patients; PPI rate 32% versus H2RA rate 62%; RR 0.50, 95%CI 0.45 to 0.56; at 12 weeks: 3 RCTs, 393 patients; PPI rate 23% versus H2RA rate 54%; RR 0.44, 95%CI 0.26 to 0.73). The rate of persistent global symptoms also was lower in the PPI group compared to H2RA group at 4 and 8 weeks (at 4w; 15 RCTs, 2941 patients; PPI rate 35% versus H2RA rate 58%; RR 0.57, 95%CI 0.48 to 0.68; at 8 weeks: 3 RCTs, 898 patients; PPI rate 32% versus H2RA rate 55%; RR 0.56, 95%CI 0.40 to 0.77). These results showed a significant heterogeneity between the trials assessed. The Clinical Evidence review found one Cochrane review (search date 2003) [3] that compared standard-doses of PPIs (omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, and pantoprazole 40 mg all once daily) versus low-doses PPIs (omeprazole 10 mg, lansoprazole 15 mg, rabeprazole 10 mg, and pantoprazole 20 mg all once daily) in patients that healed oesophagitis). At 6 to 12 months standard and low doses of PPIs significantly reduced relapse of oesophagitis and reflux symptoms compared to H2RA (standard doses PPIs - relapse of oesophagitis; 10 RCTs, 1583 patients; PPI rate 22% versus H2RA rate 58%; RR 0.36, 95%CI 0.28 to 0.46; standard doses PPIs - relapse of symptoms: 5 RCTs, 797 patients; PPI rate 22% versus H2RA rate 44%; RR 0.48, 95%CI 0.39 to 0.60; low doses PPIs - relapse of oesophagitis; 6 RCTs, 1156 patients; PPI rate 39% versus H2RA rate 66%; RR 0.57, 95%CI 0.47 to 0.69; low doses PPIs - relapse of symptoms: 4 RCTs, 831 patients; PPI rate 31% versus H2RA rate 57%; RR 0.55, 95%CI 0.47 to 0.65).
Risks	The Cochrane review [2] found no significant difference in rate of adverse effects in the initial treatment between PPIs and H2RAs (6 RCTs, 1359 patients; PPI rate 25% versus H2RA rate 26%; RR 0.92, 95%CI 0.63 to 1.36), or in the incidence of diarrhea and headache (13 RCTs, 3077 patients; PPI rate 6% versus H2RA rate 5% for diarrhea; RR 1.26, 95%CI 0.88 to 1.88; 9 RCTs, 2208 patients; PPI rate 5.5% versus H2RA rate 6.2% for headache; RR 0.98, 95%CI 0.62 to 1.53). The Cochrane review in patients that healed oesophagitis [3] found no significant difference in rate of adverse effects between standard doses of PPIs and H2RAs (3 RCTs, 469 patients; PPI rate 19% versus H2RA rate 15%; RR 1.26, 95%CI 0.89 to 1.80), but an increased rate of adverse effects between low doses of PPIs and H2RAs (3 RCTs, 574 patients; PPI rate 44% versus H2RA rate 31%; RR 1.38, 95%CI 1.11 to 1.72).
Applicability	Proton pump inhibitors are better than H2 receptor antagonists in the initial and maintenance treatment of GORD in adults. PPIs have showed a greater effect to relieve symptoms and decrease the number of patients that healed oesophagitis with a symptom relapsed, with a similar rate of adverse effects compared to H2 receptor antagonists.
Commentaries	The studies that have compared different proton pump inhibitor do not show the superiority of one specific proton pump inhibitor over the others at improving the symptoms of people with reflux oesophagitis, or to prevent relapse in symptoms in patients that healed oesaphagitis. Trials that compared esomeprazole (20 or 40mg) with omeprazole (20 mg) or pantoprazole (40 mg) found no significant differences in the rate of patients with persistent oesophagitis, healed oesophagitis, or the number of symptom episodes [1]. Some cohort studies has suggested that long-term PPIs may be associated with atrophic gastritis in people with Helicobacter pylori, but this has not been confirmed in subsequent RCT. Gastric atrophy is a risk factor for gastric cancer, however there is no reliable evidence of long-term clinical effects of PPIs on gastric cancer [1].

Costs	A study carried out in Japan [4] developed a clinical decision analysis (based in a Markov model) comparing PPI lansoprazole with H2RA ranitidine for the treatment of GORD. Lansoprazole showed a consistent superiority over ranitidine in terms of effectiveness and cost-effectiveness. The authors stated that A PPI treatment for a one-month period would improve the cost-effectiveness of this treatment.

1. Moayyedi P, Delaney B. GORD in adults. Clin Evid (Online). 2008; pii: 0403.
2. Moayyedi P, Santana J, Khan M, Preston C, Donnellan C. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD003244. DOI: 10.1002/14651858.CD003244.pub3.

3. Donnellan C, Preston C, Moayyedi P, Sharma N. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database of Systematic Reviews 2010, Issue 2. Art. No.: CD003245. DOI: 10.1002/14651858.CD003245.pub3.
4. Habu Y, Oyasu K, Wakamatsu T, Sumitomo Y, Kiyota K, Inokuchi H, Kawai K. Cost-effectiveness of the treatment of reflux esophagitis: proton pump inhibitor versus histamine-2-receptor antagonist [article in Japanese]. Nippon Rinsho. 2000;58(9):1881-5.

TABLE	GRADE Evaluation of Clinical Outcomes								
Number of Studies (N)	**Outcome**	**Comparison**	**Type of Evidence**	**Quality**	**Consistency**	**Direct Evidence**	**Size of Effect**	**GRADE**	**Comments**
26 (4032)	Symptom severity	H2RAs PPIs	4	0	-1	0	0	Moderate	Consistency reduced for high heterogeneity between RCTs
11 (1933)	Relapse rates	H2RAs PPIs	4	-1	0	0	0	Moderate	Quality reduced for incomplete outcome reporting
Type of evidence: 4 = RCT; 2 = Observational studies; 1 = Non-analytic studies / Expert opinion									