Proton Pump Inhibitors Versus Histamine 2 Receptor Antagonists for Stress Ulcer Prophylaxis in Critically Ill Patients: A Systematic Review and Meta-Analysis*

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Background: Critically ill patients may develop bleeding caused by stress ulceration. Acid suppression is commonly prescribed for patients at risk of stress ulcer bleeding. Whether proton pump inhibitors are more effective than histamine 2 receptor antagonists is unclear.

Objectives: To determine the efficacy and safety of proton pump inhibitors vs. histamine 2 receptor antagonists for the prevention of upper gastrointestinal bleeding in the ICU.

Search Methods: We searched Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, ACPJC, CINHAL, online trials registries (clinicaltrials.gov, ISRCTN Register, WHO ICTRP), conference proceedings databases, and reference lists of relevant articles.

Selection Criteria: Randomized controlled parallel group trials comparing proton pump inhibitors to histamine 2 receptor antagonists for the prevention of upper gastrointestinal bleeding in critically ill patients, published before March 2012.

Data Collection and Analysis: Two reviewers independently applied eligibility criteria, assessed quality, and extracted data. The primary outcomes were clinically important upper gastrointestinal bleeding and overt upper gastrointestinal bleeding; secondary outcomes were nosocomial pneumonia, ICU mortality, ICU length of stay, and *Clostridium difficile* infection. Trial authors were contacted for additional or clarifying information.

Results: Fourteen trials enrolling a total of 1,720 patients were included. Proton pump inhibitors were more effective than histamine 2 receptor antagonists at reducing clinically important upper gastrointestinal bleeding (relative risk 0.36; 95% confidence interval 0.19–0.68; $p = 0.002$; $I^2 = 0\%$) and overt upper gastrointestinal bleeding (relative risk 0.35; 95% confidence interval 0.21–0.59; $p < 0.0001$; $I^2 = 15\%$). There were no differences between proton pump inhibitors and histamine 2 receptor antagonists in the risk of nosocomial pneumonia (relative risk 1.06; 95% confidence interval 0.73–1.52; $p = 0.76$; $I^2 = 0\%$), ICU mortality (relative risk 1.01; 95% confidence interval 0.83–1.24; $p = 0.91$; $I^2 = 0\%$), or ICU length of stay (mean difference −0.54 days; 95% confidence interval −2.20 to 1.13; $p = 0.53$; $I^2 = 39\%$). No trials reported on *C. difficile* infection.

Conclusions: In critically ill patients, proton pump inhibitors seem to be more effective than histamine 2 receptor antagonists in preventing clinically important and overt upper gastrointestinal bleeding. The robustness of this conclusion is limited by the trial methodology, differences between lower and higher quality trials, sparse data, and possible publication bias. We observed no differences between drugs in the risk of pneumonia, death, or ICU length of stay. (*Crit Care Med* 2013; 41:693–705)

Key Words: acid suppression; gastrointestinal bleeding prophylaxis; histamine 2 receptor antagonist; proton pump inhibitor; randomized trial; stress ulcer bleeding

***See also p. 906.**

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In 1970, Skillman and Silen (1) reported a clinical syndrome of lethal "stress ulceration" in seven of 150 patients with respiratory failure, hypotension, and sepsis in the ICU. Pathologic examination demonstrated superficial ulcers confined to the gastric fundus. Subsequently, this condition was described by Lucas et al (2) in 1971 as "stress-related erosive syndrome" in 300 patients of stress-related gastrointestinal bleeding over 3 years. Overt or macroscopic gastrointestinal bleeding (hematemesis or nasogastric lavage with bright red

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blood) occurred in 5% to 25% of critically ill patients who do not receive prophylaxis in early reports (3, 4). However, the incidence of clinically important gastrointestinal bleeding is estimated to be approximately 1% to 4% at most (3, 5–7). The excess length of ICU stay attributable to clinically important upper gastrointestinal bleeding has been estimated at 4–8 days (8). In a prospective cohort study of 2,000 ICU patients, the mortality rate was 48.5% in the group with clinically important bleeding and 9.1% in the group without bleeding (5).

Several drugs for stress ulcer prophylaxis were tested in randomized trials, including histamine 2 receptor antagonists (H2RAs), sucralfate, and proton pump inhibitors (PPIs). A meta-analysis in 1996 included ten trials and found that H2RAs reduced the risk of clinically important bleeding compared with placebo (odds ratio [OR] 0.44; 95% confidence interval [CI] 0.22–0.88) (9). A recent meta-analyses comparing H2RAs to placebo included 1,836 patients from 17 trials and showed similar results (OR 0.47; 95% CI 0.29–0.76) (10). Neither meta-analysis showed a statistically significant increase in the risk of nosocomial pneumonia with H2RA administration (9, 10).

Maintaining intragastric pH above 3.5–5.0 prevents gastric mucosal injury (11). Although PPIs are more potent in increasing gastric pH compared with H2RAs (12), whether this translates into improved patient-important outcomes is unclear. Three meta-analyses comparing PPIs to H2RAs were published. In 2009, Pongprasobchai et al (13) included 569 patients from three trials. The incidence of clinically important bleeding was lower among patients receiving PPIs compared with H2RAs (OR 0.42; 95% CI 0.20–0.91). In 2010, Lin et al (14) included 936 patients from seven trials, reporting no difference in clinically important bleeding (pooled risk difference −0.04; 95% CI −0.09 to 0.01). The most recent meta-analysis by Barkun et al (15) included 1,587 patients from 13 trials and reported less clinically important bleeding with PPIs (OR 0.30; 95% CI 0.17–0.54).

The recent Surviving Sepsis Campaign guidelines recommend either H2RAs or PPIs in patients at high risk of stress ulcer bleeding (16). In a recent survey in the United Kingdom, H2RAs were chosen first by 67% of respondents followed by 20% who selected PPIs and 13% who selected sucralfate (17). In the United States, H2RAs were reportedly used as the first-line agent by 64% of 500 random intensivists, while PPIs were used by 23% (18).

We conducted an updated meta-analysis to evaluate the effect of PPIs vs. H2RAs on clinically important gastrointestinal bleeding in critically ill patients.

METHODS

Eligibility Criteria

Types of Studies. Treatment allocation by randomization and parallel control group.

Population. Adult critically ill patients (medical or surgical) in the ICU.

Intervention. Patients receiving PPIs, either parenteral or enteral, regardless of dose, frequency, and duration.

Control. Patients receiving H2RAs, either parenteral or enteral, regardless of dose, frequency, and duration.

Outcome. Bleeding was the primary outcome for this meta-analysis. Prespecified outcomes included clinically important gastrointestinal bleeding and overt upper gastrointestinal bleeding (both as defined by authors of the original trials). Secondary outcomes were nosocomial pneumonia, all-cause ICU mortality, ICU length of stay, and *Clostridium difficile* infection. For the few trials that reported only clinically important bleeding and did not report all overt bleeding, we considered clinically important bleeding to represent overt bleeding as well.

Search Strategy and Trial Identification

We conducted a search of MEDLINE (1948 to March 2012), EMBASE (1980 to March 2012), ACPJC (1991 to March 2012), Cochrane (Central) database, and CINHAL. The terms we used are included in the **online Appendix** (Supplemental Digital Content 1, http://links.lww.com/CCM/A570). We screened citations of all potentially eligible articles and searched trial registry Web sites (clinicaltrials.gov, ISRCTN Register, and WHO ICTRP). Conference proceedings were searched via Web sites provided by McMaster University (http://library.mcmaster.ca/articles/papersfirst; http://library.mcmaster.ca/articles/proceedingsfirst). No language or publication date restrictions applied. Two reviewers (W.A., F.A.) screened titles and abstracts to identify articles for full review and evaluated the full text of articles deemed potentially eligible by either reviewer.

Data Extraction

Two reviewers (W.A., F.A.) independently extracted data; disagreements were resolved by discussion and consensus. Authors were contacted for missing or unclear information.

Methodologic Quality Assessment

Trial methodologic quality was assessed using the risk of bias tool of the Cochrane Collaboration (19). For each included trial, a description, a comment, and a judgment as "low," "unclear," or "high" risk of bias was provided for each of the following items: adequate sequence generation, allocation sequence concealment, blinding for objective outcomes, incomplete outcome data, free of selective outcome reporting, and free of other bias. The overall risk of bias for an individual trial was categorized as "low" (if the risk of bias is low in all domains), "unclear" (if the risk of bias is unclear in at least one domain, with no high risk of bias domains), or "high" (if the risk of bias is high in at least one domain). The risk of bias assessment was performed by two reviewers (W.A., F.A.) independently; disagreements were resolved by discussion and consensus.

Statistical Analysis

We analyzed data using RevMan 5.1 with a random effect model. We calculated pooled relative risks for dichotomous outcomes and mean differences for continuous outcomes, with associated 95% CIs. Statistical heterogeneity was assessed by the I^2 statistic. Substantial heterogeneity was predefined as $p < 0.10$ with an $I^2 > 50\%$. The number needed to prophylax was estimated using control event rates of 2% for clinically important bleeding on H2RAs and 5% for overt bleeding on H2RAs. We used Egger's test to measure funnel plot asymmetry (20).

Subgroup Analyses

We explored heterogeneity by performing subgroup analyses to investigate a priori hypotheses potentially influencing effect size: trial methodologic quality (hypothesized to be smaller with trials of high quality), surgical vs. medical or mixed ICUs (hypothesized to be smaller in surgical patients), PPI route of administration (hypothesized to be larger with intravenous administration), PPI dose (hypothesized to be larger when used more than once daily), and geographic location of trials (hypothesized to be larger in Asian countries) (21).

Sensitivity Analyses

We conducted two sensitivity analyses. The first used risk difference as an effect estimate. Second, we excluded trials published in abstract form for which further information was unavailable (22–25).

RESULTS

Study Location and Selection

A total of 1,215 titles and abstracts were identified during primary search; after removing duplicates, 932 articles remained (**Fig. 1**). After screening the titles and abstracts, 887 articles were judged as irrelevant, 45 articles were retrieved for full assessment, and 30 were excluded for different reasons (Fig. 1). Overall, 14 randomized trials from 15 reports (one study published outcomes separately in two different journals [26, 27]) met eligibility criteria and were included. For two eligible trials in abstract form (22, 23), authors were contacted for full manuscripts.

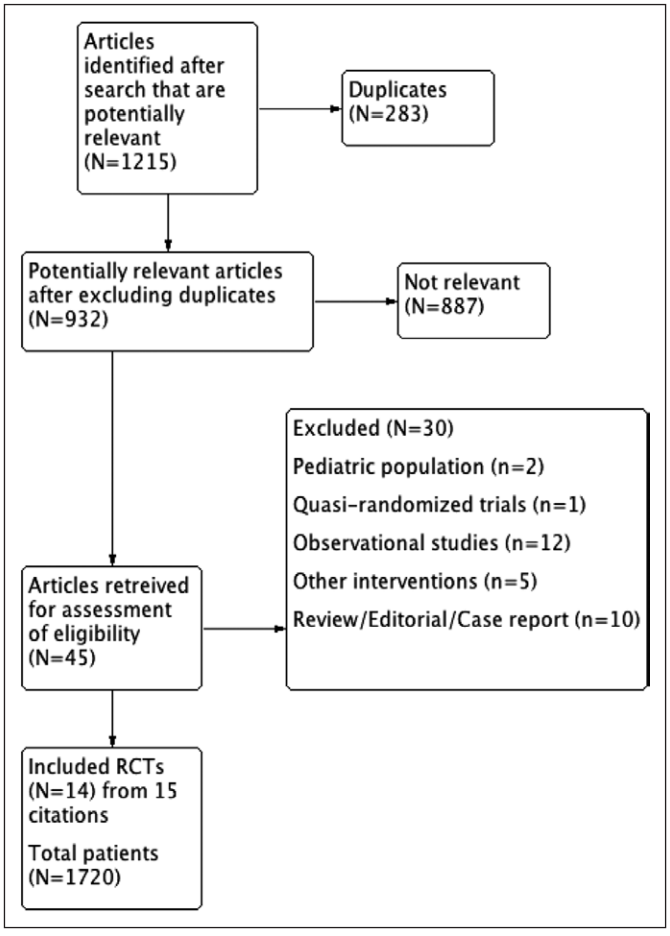

Figure 1. Flow chart showing the process of identifying eligible studies; 14 trials (four abstracts and ten fully published articles) were eligible and were included in the qualitative and quantitative analysis. RCTs = randomized controlled trials.

Publication Bias

There was asymmetry on the funnel plot in which small negative trials were missing (**Figs. 2** and **3**), which may suggest the presence of publication bias or reflect that the treatment effect is large and it is present even in the context of trials with a small number of patients. Egger's test = −1.16; 95% CI −1.68 to −0.63; $p = 0.009$, suggested the presence of publication bias for the outcome of clinically important bleeding.

Summary of Trials

Characteristics of the 14 included trials (22–36) are reported in **Table 1**. In total, 1,720 patients were enrolled with a wide

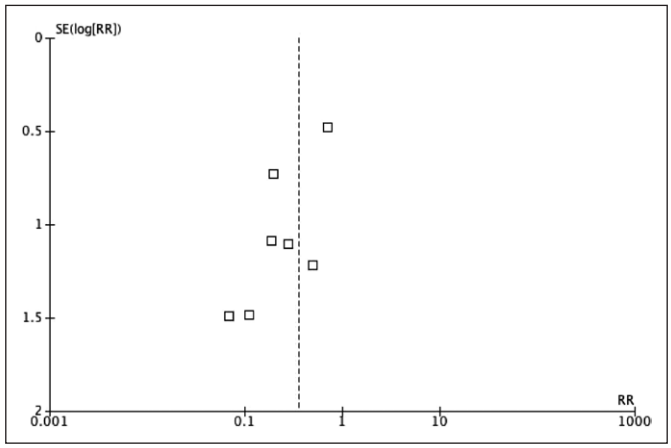

Figure 2. Funnel plot for clinically important bleeding outcome. We plotted the effect size (relative risk) against a measure of study size standard error (log RR). Visual inspection suggests asymmetry in the funnel plot, which was confirmed further by Egger's test (—1.16; 95% confidence interval, —1.68 to —0.63; $p = 0.009$).

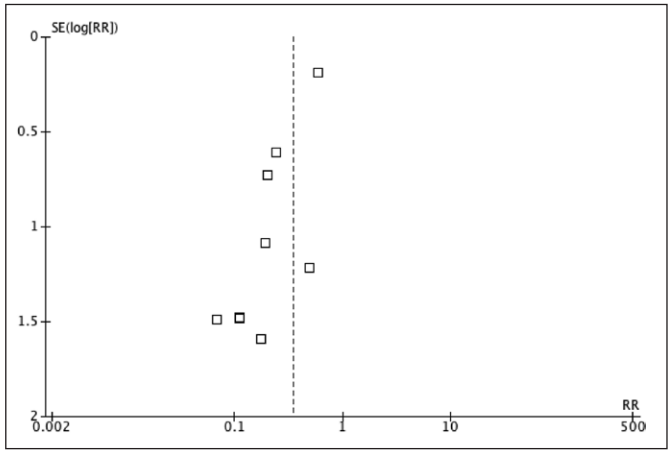

Figure 3. Funnel plot for overt bleeding outcome. We plotted the effect size (relative risk) against a measure of study size standard error (log RR). Visual inspection suggests asymmetry in the funnel plot, in which small negative studies are lacking.

TABLE 1. Characteristics of Included Trials

Author	Population	Interventions
Conrad et al (36), USA ($n = 359$)	Mechanically ventilated patients > 48 hrs, APACHE II score >11 and one more risk factor for stress ulcers. Age (mean): 55.6; male: 59%; APACHE II (mean): 23.7	Omeprazole suspension 40 mg NG twice daily loading, then 40 mg NGT daily ($n = 178$); cimetidine 300 mg IV bolus, then infusion at 50 mg/hr ($n = 181$)
Azevedo et al (28); Brazil ($n = 108$)	Critically ill patients with at least one risk factor for stress ulcers. Age (mean): 56.7 yrs; male: 52%; APACHE (mean): 55.3	Omeprazole 40 mg IV twice daily ($n = 38$); ranitidine 150 mg/day infusion ($n = 38$); sucralfate 1 g NG four times daily ($n = 32$)
Hata et al (30), Japan ($n = 210$)	Post open cardiac surgery patients at risk of stress ulcers. Age (mean): 64.5 yrs; male: 73%; APACHE II: N/A	Rabeprazole PO 10 mg daily ($n = 70$); ranitidine PO 300 mg daily ($n = 70$); teprenone 150 mg NG daily ($n = 70$)
Kantorova et al (35); Czech Republic ($n = 287$)	Patients who had a major surgery who are admitted to surgical ICU and have one of the following: mechanical ventilation >48 hrs or coagulopathy. Age (mean): 47 yrs; male: 67%; APACHE II (mean): 18.4	Omeprazole 40 mg IV daily ($n = 72$); famotidine 40 mg IV twice daily ($n = 71$); sucralfate 1 g NG four times daily ($n = 69$); placebo ($n = 75$)
Kotlyanskaya et al (22) (Abstract); USA ($n = 66$)	Medical ICU all patients mechanically ventilated with additional risk factors for stress ulcers. Age (mean): 71.2 yrs; male: N/A; APACHE II (mean): 27.6	Lansoprazole (suspension) NG ($n = 22$); lansoprazole (tablet) NG ($n = 23$); ranitidine ($n = 21$) (dose and frequency not reported)
Levy et al (29); USA ($n = 67$)	Medical and surgical ICU patients with at least one risk factor for stress ulcers. Age (mean): 57.1 yrs; male: 55%; APACHE II (mean): 18.9	Omeprazole 40 mg NG daily ($n = 32$); tanitidine 50 mg IV bolus, then 150 mg IV daily ($n = 35$)
Pan et al (31); China ($n = 30$)	Critically ill patients with severe acute pancreatitis. Age (mean): 48 yrs; male: 45%; APACHE II (mean): 12.2	Rabeprazole PO 20 mg once daily ($n = 20$); famotidine IV 40 mg twice daily ($n = 10$)
Phillips and Metzler (23) (Abstract); USA ($n = 58$)	Critically ill patients who are mechanically ventilated and have another risk factor for bleeding Age: N/A; male: N/A; APACHE II: N/A	Omeprazole 40 mg NGT loading, then 20 mg NGT daily ($n = 33$); ranitidine 50 mg IV loading, then 150–200 mg/day infusion ($n = 25$)
Powell et al (33); UK ($n = 41$)	Post coronary artery bypass graft patients in surgical ICU. Age (mean): 56.5 yrs; male: 86%; APACHE II (mean): N/A	Omeprazole 80 mg IV bolus, then 40 mg IV bolus three times daily ($n = 10$); omeprazole 80 mg IV bolus then 40 mg IV infusion three times daily ($n = 10$); ranitidine 50 mg IV three times daily ($n = 11$); placebo ($n = 10$)
Risaliti et al (32); Italy ($n = 28$)	Patients post major surgery in surgical ICU. Age (mean): 61.5 yrs; male: 64%; APACHE II: N/A	Omeprazole 40 mg daily IV, then 20 mg PO daily ($n = 14$); ranitidine 150 mg IV daily, then 300 mg PO daily ($n = 14$)
Solouki et al (26, 27); Iran ($n = 129$)	Critically ill patients who required MV for > 48 hrs and other risk factor for stress ulcers. Age (mean): 50.8 yrs; male: 52%; APACHE II: N/A	Omeprazole 20 mg NG twice daily ($n = 61$); ranitidine 50 mg IV twice daily ($n = 68$)
Somberg et al (34); USA ($n = 202$)	Medical and surgical ICU patients with at least one risk factor for stress ulcers. Age (mean): 42 yrs; male: 74%; APACHE II (mean): 15.2	Pantoprazole 40 mg IV daily ($n = 32$); pantoprazole 40 mg IV twice daily ($n = 38$); pantoprazole 80 mg IV daily ($n = 23$); pantoprazole 80 mg IV twice daily ($n = 39$); pantoprazole 80 mg IV three times daily ($n = 35$); cimetidine 300 mg IV bolus, then 50 mg/h infusion ($n = 35$)

(*Continued*)

Outcomes	Definition of Gastrointestinal Bleeding	Funding
Clinically important bleeding; overt bleeding; pneumonia; mortality	a) Bright red blood not clearing after tube adjustment and lavage with saline for 5–10 mins; b) 8 hrs of persistent gastro-occult positive coffee grounds material with aspirates every 2 hrs not clearing with lavage; or c) Persistent gastro-occult positive coffee grounds material over 2–4 hrs on d 3–14 in three consecutive aspirates not clearing with lavage	Supported by Santarus
Overt bleeding; nosocomial pneumonia; mortality; ICU length of stay	Upper gastrointestinal bleeding including hematemesis, bright red blood, coffee ground emesis or melena	Not reported
Overt bleeding; adverse events	Upper gastrointestinal bleeding (hematemesis, coffee grounds emesis, or melena) confirmed with gastrodudenoscopy	Not reported
Clinically important bleeding; nosocomial pneumonia; mortality; ICU length of stay; adverse events	Overt bleeding with one of the following: a) Drop in systolic blood pressure >20 mm Hg or rise in pulse rate > 20 beats/min within 24 hrs of the onset of bleeding not explained by other causes; or b) Drop in hemoglobin by 2 g/dL or more not explained by other causes	Supported by Internal Grant Agency of the Czech Republic Ministry of Health
Clinically important bleeding; overt bleeding; nosocomial pneumonia; drug adverse events	Overt bleeding associated with change in hemodynamics or drop in the hemoglobin	Not reported
Clinically important bleeding; nosocomial pneumonia; mortality; ICU length of stay	Hemodynamic instability resulting from gross bleeding as manifest by hematemesis, aspiration of coffee ground material from the nasogastric tube, or melena, or a decrease in hemoglobin of >2 g/dL complicated by either the need for transfusion or hemodynamic instability	Not reported
Overt bleeding	Melena or hematemesis	Not reported
Clinically important bleeding; pneumonia; adverse events	No clear definition	Not reported
Clinically important bleeding; mortality	Bloody nasogastric tube aspirate	ASTRA clinical research unit
Clinically important bleeding; overt bleeding; adverse events	No clear definition	Not reported
Clinically important bleeding; nosocomial pneumonia; mortality; ICU length of stay	Overt bleeding associated with one of the following: a) A 20 mm Hg decrease in systolic or diastolic blood pressure during the first 24 hrs after bleeding; b) A 20 beat/min increase in heart rate or 10 mm Hg in systolic blood pressure in a standing position; c) A 2 g/dL decrease of hemoglobin or 6% decrease in hematocrit during the first 24 hrs after bleeding; d) Lack of increase in hemoglobin after infusing two units of packed cells	Not reported
Clinically important bleeding; pneumonia; mortality; adverse events	a) Hematemesis or bright red blood in gastric aspirate that did not clear after adjustment of nasogastric or orogastric tube and a 5- to 10-min lavage with iced water or saline; b) Persistent coffee ground material for eight consecutive hours that did not clear with a 100 mL lavage, or was accompanied bya 5% decrease in hematocrit; c) A decrease in hematocrit requiring one or more transfusions that occurred in the absence of any obvious source and required further diagnostic studies; or d) Melena or frank bloody stools from an upper gastrointestinal source	Supported by Wyeth Pharmaceuticals

(*Continued*)

TABLE 1. (*Continued*) Characteristics of Included Trials

Author	Population	Interventions
Fink et al (24) (Abstract); USA ($n = 189$)	Adult critically ill patients. Acute Physiology Score II (mean): 15	(4:1) Randomization as follows: IV pantoprazole 40 mg daily, 40 mg twice daily, 80 mg daily, or 80 mg twice daily ($n = 158$); IV cimetidine 300 mg bolus, then 50 mg/hr infusion ($n = 31$)
Morris (25) (Abstract); USA ($n = 202$)	Adult critically ill patients at risk of UGI bleeding	(5:1) Randomization as follows: IV pantoprazole 40 mg daily, 40 mg twice daily, 80 mg daily, 80 mg twice daily, or 80 mg three times daily ($n = 169$); IV cimetidine 300 mg IV loading, then 50 mg/hr ($n = 33$)

APACHE II = Acute Physiological and Chronic Health Evaluation II; NG = nasogastric; NGT = nasogastric; PO = by mouth; N/A = not applicable; UGI = upper gastrointestinal.

This table describes the populations, interventions, outcomes, and funding source of included trials. It also provides information on the trial setting and number of
patients included.

spectrum of medical and surgical illnesses and at least one risk factor for stress ulcer bleeding. The variable bleeding definitions are outlined in Table 1.

Assessment of Methodologic Quality

Using the Cochrane risk of bias tool, three trials were judged to be at low risk of bias, and five trials were considered to be in the unclear risk of bias category (**Table 2**). We could not fully assess the quality of the four trials published as abstracts without the full manuscripts (22–25). Six trials were in the high risk of bias category, mostly because of the lack of appropriate blinding. The GRADE (37) approach was also used to assess quality of evidence for individual outcomes; results are presented in the evidence profile table (**Table 3**).

Clinically Important Bleeding

Twelve trials enrolling 1,614 patients reported clinically important bleeding (**Fig. 4**). PPIs were associated with a lower risk of clinically important bleeding compared with H2RAs relative risk [RR] 0.36; 95% CI 0.19–0.68; $p = 0.002$; $I^2 = 0\%$). The number needed to prophylax is estimated at 78 using a control event rate of 2%.

Overt Bleeding

Fourteen trials enrolling 1,720 patients reported overt upper gastrointestinal bleeding (**Fig. 5**). All studies had a sensible definition of overt bleeding (coffee ground emesis, hematemesis, melena, or hematochezia from presumed upper gastrointestinal source). PPIs were associated with a lower risk of overt bleeding when compared with H2RA (RR 0.35; 95% CI 0.21–0.59; $p < 0.0001$; $I^2 = 15\%$). The number needed to prophylax is estimated at 30 using a control event rate of 5%.

Nosocomial Pneumonia

Eight trials enrolling 1,100 patients reported nosocomial pneumonia (**Fig. 6**). There was no difference between groups in the risk of nosocomial pneumonia (RR 1.06; 95% CI 0.73–1.52; $p = 0.76$; $I^2 = 0\%$).

Mortality

Eight trials enrolling 1,196 patients reported mortality, usually recorded as ICU mortality or 28-day mortality (**Fig. 7**). There was no difference between groups in risk of death (RR 1.01; 95% CI 0.83–1.24; $p = 0.91$; $I^2 = 0\%$).

ICU Length of Stay

Five trials enrolling 555 patients reported ICU length of stay (**Fig. 8**). There was no difference between groups in ICU length of stay (mean difference −0.54 days; 95% CI −2.20 to 1.13; $p = 0.53$; $I^2 = 39\%$).

Clostridium difficile Infection

No trials reported on *C. difficile* infection.

Subgroup Analyses

Although heterogeneity was not large, we proceeded to perform our a priori subgroup analyses to test the robustness of findings for clinically important bleeding and overt bleeding.

Of the 14 included trials, only three were judged to be at low risk of bias, six trials were at high risk of bias, and five had unclear risk of bias. There was a statistically significant difference between low risk of bias trials vs. other trials at high risk or unclear risk of bias with regard to both risk of clinically important bleeding ($p = 0.05$ for interaction) and overt bleeding ($p = 0.03$ for interaction), such that higher quality trials were associated with a smaller treatment effect (**Fig. 9**).

We found no clear subgroup differences regarding either clinically important bleeding or overt bleeding when comparing intravenous vs. enteral route of PPI administration, frequency of PPI dosing (once vs. more than once daily), ICU type (surgical ICU vs. medical or mixed ICU), or trial setting (Asian vs. non-Asian). The results including p values for interactions are summarized in **Tables 4** and 5.

Outcomes	Definition of Gastrointestinal Bleeding	Funding
UGI bleeding; mortality	No clear definition	Not reported
UGI bleeding; nosocomial pneumonia	No clear definition	Not reported

TABLE 2. Methodologic Quality of Trials

Author	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting Bias	Free of Other Bias	Overall Risk of Bias
Conrad et al (36)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Azevedo et al (28)	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Hata et al (30)	Low risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Kantorova et al (35)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Kotlyanskaya et al (22)	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Levy et al (29)	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Pan et al (31)	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	High risk of bias
Phillips and Metzler (23)	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias
Powell et al (33)	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias
Risaliti et al (32) 1993	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias
Solouki et al (26, 27)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Somberg et al (34)	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Fink et al (24)	Unclear risk of bias	Unclear risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias
Morris (25)	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias	Unclear risk of bias

In this table, the methodologic quality of each trial using the Cochrane Risk of Bias Tool is summarized. In each category judgment for risk of bias to be low, unclear, or high is indicated. The overall risk of bias for each trial is provided.

TABLE 3. Evidence Profile Using GRADE Approach

Quality Assessment					
No. of Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**
Clinically important bleeding					
12	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]
Overt upper gastrointestinal bleeding					
14	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision
Mortality					
8	Randomized trials	Serious	No serious inconsistency	No serious indirectness	No serious imprecision
Nosocomial pneumonia					
8	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision

This table is generated using the GRADEprofiler software that summarizes the quality of evidence for individual outcomes based on five main domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. For each outcome, the quality of evidence is presented along with the clinical importance of the outcome.

[a]Downgraded for risk of bias mainly due to lack of or incomplete blinding.

[b]Downgraded for low number of events rather than confidence interval.

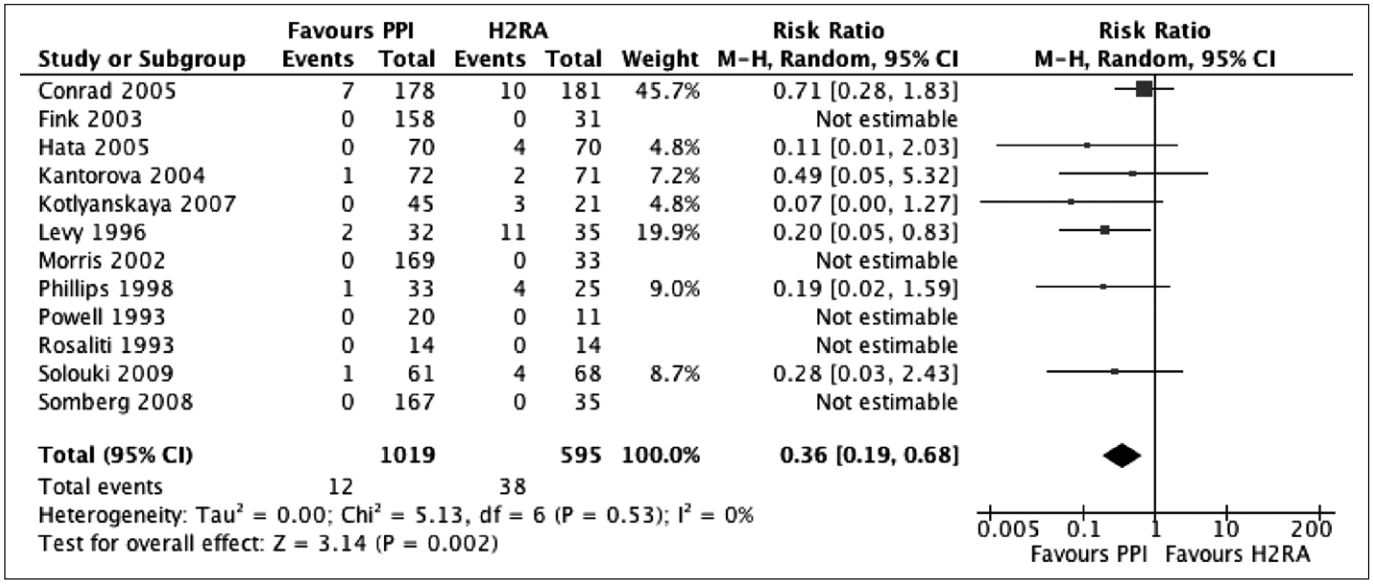

Figure 4. Forrest plot for clinically important gastrointestinal bleeding outcome. Data from 12 trials were included in the analysis using random effects model. The use of proton pump inhibitor (PPI) was associated with a significantly lower risk of clinically important bleeding compared with histamine 2 receptor antagonist (H2RA) (risk ratio [the same as relative risk] [RR] 0.36; 95% confidence interval [CI] 0.19–0.68). M-H = Mantel Haenszel.

Sensitivity Analysis

Sensitivity analysis was conducted examining the effect of using risk difference as an estimate of effect for clinically important bleeding (risk difference −0.03; 95% CI −0.05 to 0.00, p = 0.06, I^2 = 52%) and overt bleeding (risk difference −0.06; 95% CI −0.11 to −0.02, p = 0.009, I^2 = 80%), although significant heterogeneity was present. The second sensitivity analysis excluded trials published in abstract form (22–25). Clinically important bleeding (RR 0.42; 95% CI 0.21–0.84; p = 0.01; I^2 = 0%) and overt bleeding (RR 0.40; 95% CI 0.25–0.67; p = 0.0004; I^2 = 12%) were significantly reduced, consistent with the main analysis.

DISCUSSION

In this meta-analysis, we found that PPIs were more effective than H2RAs at preventing clinically important bleeding and overt gastrointestinal bleeding. The main reservation about using PPIs

No. of Patients		Effect			
Proton Pump Inhibitor	Histamine 2 Receptor Antagonist	Relative (95% Confidence Interval)	Absolute	Quality	Importance
12/1019 (1.2%)	38/595 (6.4%)	RR 0.36 (0.19–0.68)	46 fewer per 1000 (from 23 fewer to 58 fewer)	Low	Critical
41/1077 (3.8%)	101/643 (15.7%)	RR 0.35 (0.21–0.59)	113 fewer per 1000 (from 72 fewer to 138 fewer)	Moderate	Important
127/726 (17.5%)	100/470 (21.2%)	RR 1.01 (0.83–1.24)	0 fewer per 1000 (from 42 fewer to 51 more)	Moderate	Critical
66/626 (10.5%)	50/474 (10.5%)	RR 1.06 (0.73–1.52)	6 more per 1000 (from 28 fewer to 55 more)	Moderate	Critical

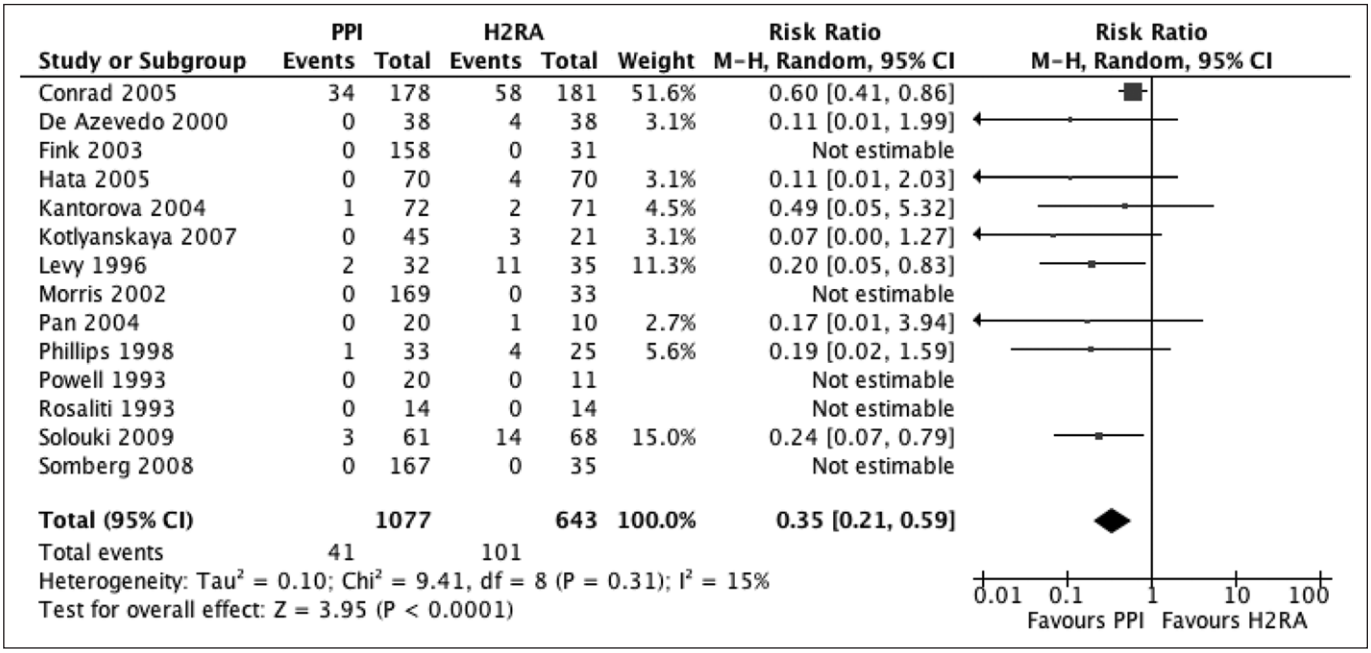

Figure 5. Forrest plot for overt upper gastrointestinal bleeding outcome. Data from 14 trials were included in the analysis using random effects model. The use of proton pump inhibitor (PPI) was associated with a significantly lower risk of overt bleeding compared with histamine 2 receptor antagonist (H2RA) (risk ratio [the same as relative risk] [RR] 0.35; 95% confidence interval [CI] 0.21–0.59). M-H = Mantel Haenszel.

in the critical care setting rather than H2RAs is the potential to increase the incidence of nosocomial pneumonia (38, 39); however, trials do not suggest such a difference. Mortality and length of ICU stay were not affected. None of the trials reported *C. difficile* infection, although a systematic review of 12 observational studies evaluating 2,948 patients with *C. difficile* found an association with antisecretory therapy (OR 1.94; 95% CI 1.37–2.75). The association was present for PPI use (OR 2.05; 95% CI 1.47–2.85) and for H2RA use (OR 1.47; 95% CI 1.06–2.05), with no difference between PPIs and H2RAs ($p = 0.17$) (40).

There was no heterogeneity of results in this meta-analysis. Subgroup analyses examining dosing and frequency of PPI administration, and specific populations (medical vs. surgical ICU patients, and Asian vs. non-Asian patients) showed no sig-

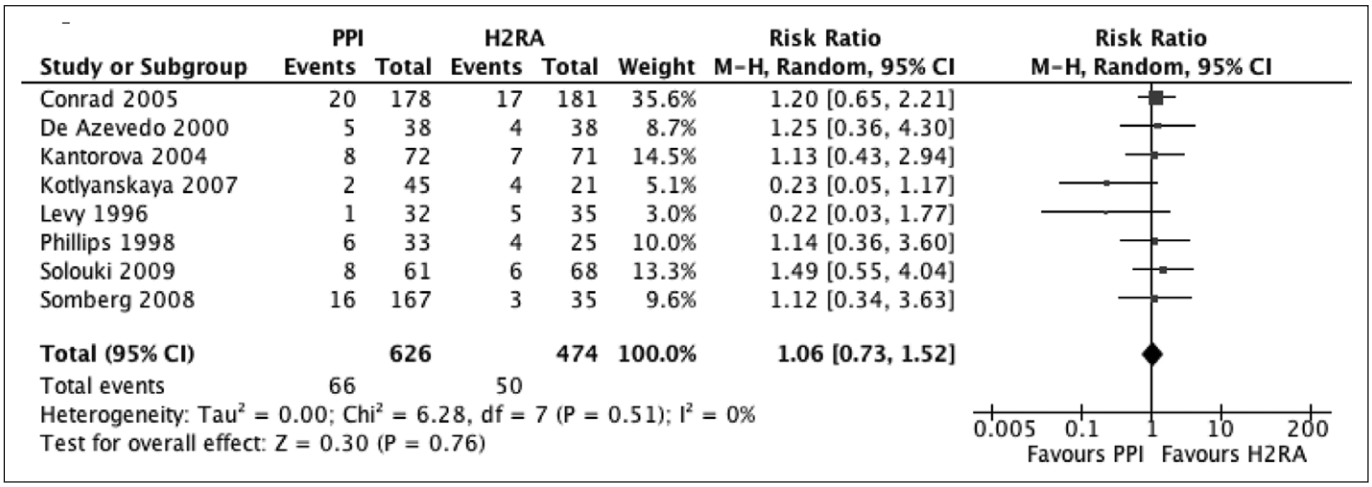

Figure 6. Forrest plot for nosocomial pneumonia outcome. Data from eight trials were included in the analysis using random effects model. The risk of nosocomial pneumonia was similar in both groups risk ratio [the same as relative risk] [RR] 1.06; 95% confidence interval [CI] 0.73–1.52). H2RA = histamine 2 receptor antagonist; M-H = Mantel Haenszel; PPI = proton pump inhibitor.

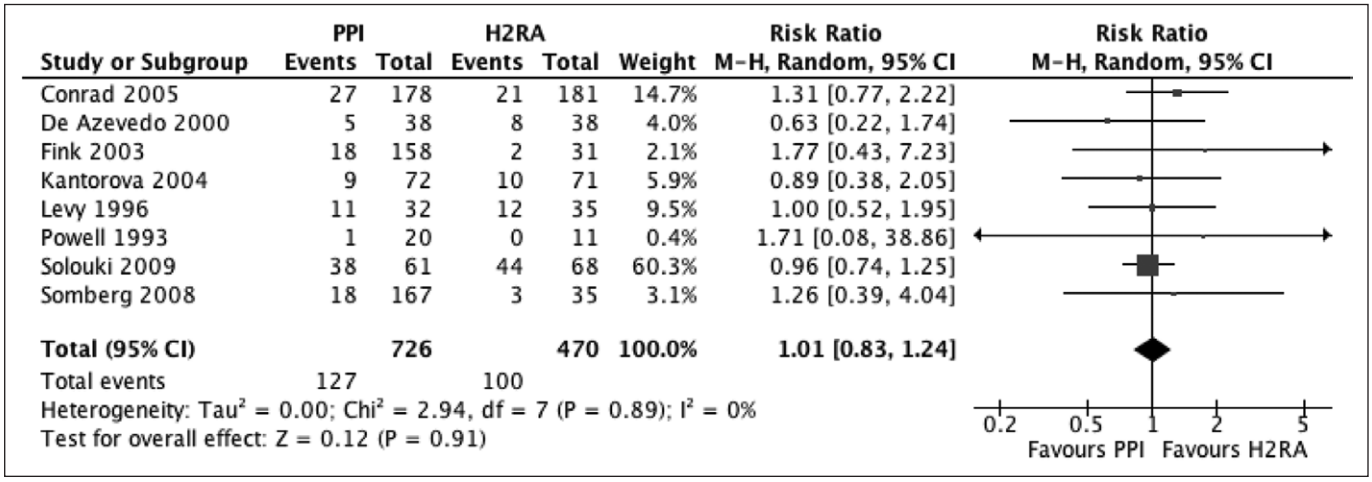

Figure 7. Forrest plot for ICU mortality outcome. Data from eight trials were included in the analysis using random effects model. The risk of death during the ICU stay was similar in both groups (risk ratio [the same as relative risk] [RR] 1.01; 95% confidence interval [CI] 0.83–1.24). H2RA = histamine 2 receptor antagonist; M-H = Mantel Haenszel; PPI = proton pump inhibitor.

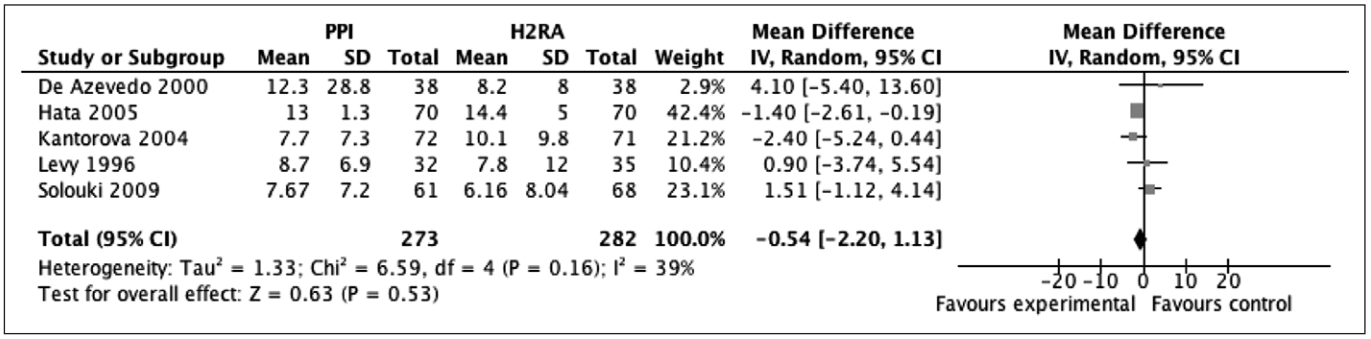

Figure 8. Forrest plot for ICU length of stay outcome. Data from five trials were included in the analysis using random effects model. There was no statistically significant difference between groups (weighted mean difference –0.54; 95% confidence interval [CI] –2.20 to 1.13). H2RA = histamine 2 receptor antagonist; PPI = proton pump inhibitor.

nificant differences. We included all identified trials conducted in the critical care setting, enhancing the generalizability of these findings.

Nevertheless, several factors suggest cautious interpretation of these results. First, the risk of bias for included trials was variable across trial quality domains and across trials, and subgroup analysis based on trial quality suggested that the treatment effect was smaller in trials of higher quality. It is thus possible that suboptimal trial design, especially the lack of blinding, has inflated the observed benefits of PPIs. The possibility that the efficacy of PPI therapy has been overestimated by publication bias is also supported by funnel plot asymmetry with the absence of small negative studies. The

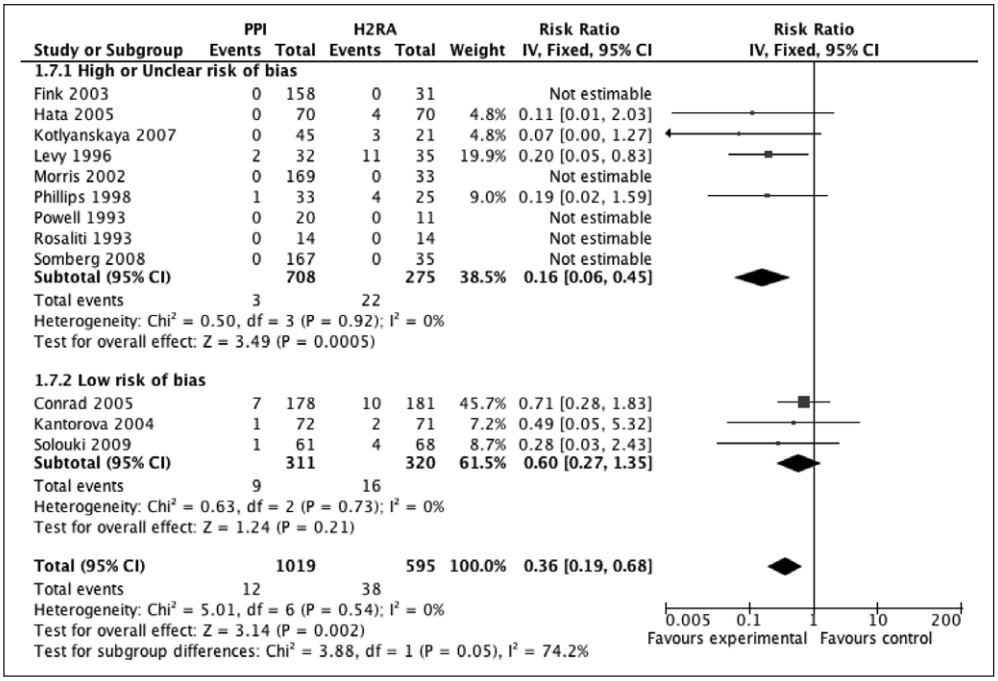

Figure 9. Forrest plot for subgroup analysis: low risk of bias studies vs. high or unclear risk of bias studies for clinically important bleeding outcome. This analysis conducted using inverse variance method and fixed effect to test subgroup difference. The test for subgroup difference suggested a difference between both subgroups ($p = 0.05$) and $I^2 = 74.2\%$ (which represents heterogeneity between subgroups). CI = confidence interval; H2RA = histamine 2 receptor antagonist; PPI = proton pump inhibitor; RR = risk ratio (the same as relative risk).

TABLE 4. Subgroup Analyses for Clinically Important Bleeding Outcome

Subgroup	Subtotal, *n*	Relative Risk (95% Confidence Interval)	*p* (Interaction Between Groups)	I^2 (Heterogeneity Between Groups)
Methodologic quality of studies			0.05	74.2%
Low risk of bias	631	0.60 (0.27–1.35)		
High/unclear risk of bias	983	0.16 (0.06–0.45)		
ICU type			0.83	0%
Surgical ICU	342	0.26 (0.06–1.33)		
Medical/mixed	1272	0.32 (0.18–0.65)		
Route of proton pump inhibitor			0.79	0%
Enteral	847	0.35 (0.18–0.68)		
Parentral	767	0.36 (0.19–0.68)		
Frequency of proton pump inhibitor			0.75	0%
Once daily	795	0.40 (0.20–0.80)		
More than once daily	753	0.39 (0.20–0.75)		
Geographic location of studies			0.76	0%
Non-Asian	1345	0.39 (0.20–0.73)		
Asia	299	0.28 (0.03–2.43)		

In this table, the subgroup analyses are summarized. The measure of treatment effect is provided for each subgroup and the interaction *p* value and I^2 for subgroup difference. All analyses were conducted using the inverse variance and fixed effect model.

TABLE 5. Subgroup Analyses for Overt Upper Gastrointestinal Bleeding Outcome

Subgroup	Subtotal, *n*	Relative Risk (95% Confidence Interval)	*p* (Interaction Between Groups)	I^2 (Heterogeneity Between Groups)
Methodologic quality of studies			0.03	78.2%
Low risk of bias	631	0.58 (0.25–1.36)		
High/unclear risk of bias	1089	0.13 (0.04–0.38)		
ICU type			0.82	0%
Surgical ICU	342	0.27 (0.04–1.71)		
Medical/mixed	1378	0.34 (0.18–0.65)		
Route of proton pump inhibitor			0.81	0%
Enteral	877	0.34 (0.18–0.65)		
Parentral	843	0.27 (0.04–1.69)		
Frequency of proton pump inhibitor			0.45	0%
Once daily	825	0.39 (0.20–0.76)		
More than once daily	829	0.20 (0.04–1.13)		
Geographic location of studies			0.45	0%
Non-Asian	1421	0.37 (0.19–0.72)		
Asia	299	0.19 (0.04–0.88)		

In this table, the subgroup analyses are summarized. The measure of treatment effect is provided for each subgroup and the interaction *p* value and I^2 for subgroup difference. All analyses were conducted using the inverse variance and fixed effect model.

primary outcome of clinically important bleeding was necessarily defined by the authors of each trial and contributed to the variable incidence. One rate was as high as 31%, which seems implausibly large compared with current clinical experiences (29). The small number of events is also a concern. Definitions of pneumonia also varied across trials; either random or systematic error in pneumonia ascertainment could attenuate treatment differences if they do exist. A subgroup analysis from a systematic review comparing H2RAs vs. placebo suggested that patients not receiving enteral nutrition, compared with those receiving it, may be more likely to benefit from acid suppression (10). However, no trials in this meta-analysis randomized patients to nutritional strategies, or stratified randomization based on initial nutritional strategy, or provided direct data on the influence of enteral nutrition on gastrointestinal bleeding.

Three previous meta-analyses used different methods and yielded some different conclusions. Lin et al (14) used risk difference as an effect measure, a metric markedly affected by trials with very few or no events, such that it decreases the ability to detect a treatment effect and is not advised in that situation (41). The meta-analyses by Pongprasobchai et al (13) and Barkun et al (15) suggested that PPIs are superior to H2RAs for bleeding prevention. Resolving discordant meta-analyses (42), our search identified more trials, and we excluded quasi-randomized trials (43), which others did not (15). We examined the effect of methodologic quality on overall results and used the more conservative random rather than fixed effect model.

In summary, this meta-analysis provides a comprehensive summary of available trial information for clinicians and guideline developers, suggesting that PPIs, compared with H2RAs, may significantly lower the risk of clinically important and overt gastrointestinal bleeding in critically ill patients, without influencing the risk of nosocomial pneumonia, ICU mortality, or length of ICU stay. Meanwhile, rigorous research is welcome on current gastrointestinal bleeding rates hypothesized to be lower in today's practice, potentially reduced recently by optimal resuscitation (7, 44) and early enteral nutrition (10), which would increase the number needed to prophylax to prevent a bleed, and correspondingly, increase the cost per event averted. The role of acid suppression predisposing to *C. difficile* infection in the ICU also warrants further investigation as no trials to date have examined this outcome.

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