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Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To determine, in critically ill patients, the relative impact of proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, or no gastrointestinal bleeding prophylaxis (or stress ulcer prophylaxis) on outcomes important to patients.

DESIGN

Systematic review and network meta-analysis.

DATA SOURCES

Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, trial registers, and grey literature up to March 2019.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES AND METHODS

We included randomised controlled trials that compared gastrointestinal bleeding prophylaxis with PPIs, H2RAs, or sucralfate versus one another or placebo or no prophylaxis in adult critically ill patients. Two reviewers independently screened studies for eligibility, extracted data, and assessed risk of bias. A parallel guideline committee (*BMJ* Rapid Recommendation) provided critical oversight of the systematic review, including identifying outcomes important to patients. We performed random-effects pairwise and network meta-analyses and used GRADE to assess certainty of evidence for each outcome. When results differed between low risk and high risk of bias studies, we used the former as best estimates.

RESULTS

Seventy two trials including 12 660 patients proved eligible. For patients at highest risk (>8%) or high risk (4-8%) of bleeding, both PPIs and H2RAs probably reduce clinically important gastrointestinal bleeding compared with placebo or no prophylaxis (odds ratio for PPIs 0.61 (95% confidence interval 0.42 to 0.89), 3.3% fewer for highest risk and 2.3% fewer for high risk patients, moderate certainty; odds ratio for H2RAs 0.46 (0.27 to 0.79), 4.6% fewer for highest risk and 3.1% fewer for high risk patients, moderate certainty). Both may increase the risk of pneumonia compared with no prophylaxis (odds ratio for PPIs 1.39 (0.98 to 2.10), 5.0% more, low certainty; odds ratio for H2RAs 1.26 (0.89 to 1.85), 3.4% more, low certainty). It is likely that neither affect mortality (PPIs 1.06 (0.90 to 1.28), 1.3% more, moderate certainty; H2RAs 0.96 (0.79 to 1.19), 0.9% fewer, moderate certainty). Otherwise, results provided no support for any affect on mortality, *Clostridium difficile* infection, length of intensive care stay, length of hospital stay, or duration of mechanical ventilation (varying certainty of evidence).

CONCLUSIONS

For higher risk critically ill patients, PPIs and H2RAs likely result in important reductions in gastrointestinal bleeding compared with no prophylaxis; for patients at low risk, the reduction in bleeding may be unimportant. Both PPIs and H2RAs may result in important increases in pneumonia. Variable quality evidence suggested no important effects of interventions on mortality or other in-hospital morbidity outcomes.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42019126656.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Most patients at high risk of gastrointestinal bleeding receive acid suppression during a stay in intensive care

The practice of gastrointestinal bleeding prophylaxis (often referred to as stress ulcer prophylaxis) has generated controversy

WHAT THIS STUDY ADDS

For higher risk critically ill patients, PPIs and H2RAs likely result in important reductions in gastrointestinal bleeding compared with no prophylaxis; for patients at low risk, the reduction in bleeding may be unimportant

Both PPIs and H2RAs may increase the risk of pneumonia

Evidence failed to support differences in a number of outcomes, including mortality

Introduction

Critically ill patients in intensive care units are at risk of gastrointestinal bleeding (for example, from stress ulceration).[1] Authorities have suggested gastrointestinal bleeding prophylaxis is necessary to optimise the care of critically ill patients (often referred to as stress ulcer prophylaxis). Most patients at high risk receive acid suppression during intensive care.[2 3] Proton pump inhibitors (PPIs) are the most common prophylactic agent, followed by histamine-2 receptor antagonists (H2RAs); clinicians seldom use sucralfate and antacids.[2 4]

Many published systematic reviews and meta-analyses have summarised randomised controlled trial evidence addressing the efficacy and safety of interventions for gastrointestinal bleeding prophylaxis,[5-10] including a network meta-analysis conducted by members of our team.[5] Results provided support for prophylaxis, but raised concerning issues, particularly

nosocomial pneumonia. Much of the releveant evidence was, however, of low or very low quality.

Since the publication of the last network meta-analysis, several trials have been published,[11-14] including a large, international, multicenter randomised controlled trial (the SUP-ICU trial).[14] This trial compared pantoprazole with placebo and concluded that pantoprazole did not reduce mortality or a composite secondary outcome of "clinically important events" and questioned the routine use of PPIs in critically ill adults.

Because of new evidence suggesting a decrease in the frequency of bleeding, and new awareness of the possible limited morbidity associated with many bleeds, the practice of gastrointestinal bleeding-prophylaxis has generated controversy.[15] Moreover, observational studies have reported substantial increases in nosocomial pneumonia and *Clostridium difficile* infection with the use of acid-suppressive drugs,[16 17] raising concern that harms may outweigh benefits.

We conducted an updated systematic review and network meta-analysis on the potential benefits and harms of gastrointestinal bleeding prophylaxis with PPIs, H2RAs, and sucralfate in critically ill patients. This review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. The aim of the project is to respond to new, potentially practice-changing evidence and provide a trustworthy practice guideline in a timely manner underpinned by best evidence.[18] In this case, the stimulus was the SUP-ICU trial.[14] This systematic review informs a *BMJ* Rapid Recommendation (box 1).

Methods

Protocol registration

We registered the protocol for this systematic review with PROSPERO (CRD42019126656).

Guideline panel and patient involvement

In accordance with the *BMJ* Rapid Recommendations process, a guideline panel provided critical oversight during the review process, which included identifying populations, subgroups, and outcomes of interest. The guideline panel consisted of content experts, criti cal care clinicians, gastroenterologist, pharmacists, methodologists, former patients, and a patient care giver. Patients received personal training and support to optimise contributions throughout the guideline development process.

Search strategy

Our literature search, developed in collaboration with a research librarian, added the brand, generic and experimental names of PPIs, H2RAs, and sucralfate to the original search terms from our previous network meta-analysis (see appendix 1 on bmj.com). The search included Medline and Embase, the Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov from January 2017 to March 2019 (our previous network meta-analysis searched from inception to April 2017), and a PubMed search for studies not yet indexed or not found in Medline and Latin American and Caribbean Health Sciences Literature (LILACS). Reviewers also searched the abstracts of the past two years of proceedings for the following conferences: Digestive Disease Week, United European Gastroenterology Week, European Society of Intensive Medicine, and Society of Critical Care Medicine. The reviewers scanned the reference lists of included studies and relevant systematic reviews to identify potential eligible studies.

Study selection

Two reviewers independently performed the study selection, including screening titles and abstracts, and evaluating full-text eligibility of potentially eligible studies. Reviewers resolved disagreements by discussion or by consultation with a third reviewer.

We included randomised controlled trials that compared the efficacy and safety of gastrointestinal bleeding prophylaxis, PPIs, H2RAs, or sucralfate versus one another or placebo or no prophylaxis in adult critically ill patients at risk of gastrointestinal bleeding regardless of location. We did not contact authors of studies, and we excluded studies that did not report sufficient information to pool data (for example, uncertain number of events or number of patients in each group). We applied no restriction based on dose or route of administration, duration of prophylaxis, or language of publication.

Outcomes included mortality at the longest follow-up reported, clinically important gastrointestinal bleeding, pneumonia, *C difficile* infection, overt gastrointestinal bleeding, length of stay in intensive care, length of hospital stay, and duration of mechanical ventilation. We accepted study definitions of overt bleeding, typically defined as hematemesis, melaena, haematochezia, or coffee-grounds emesis or aspirate without additional characteristics of clinically important gastrointestinal bleeding. We accepted study definitions of clinically important gastrointestinal bleeding, which typically included evidence of upper gastrointestinal bleeding with any of the following: significant haemodynamic changes not explained by other causes, need for transfusion of more than two

Box 1: Linked resources in this BMJ Rapid Recommendations cluster

- Ye Z, Blaser AR, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ* 2019;367:l6722
  - Summary of the results from the Rapid Recommendation process
- Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. *BMJ* 2019;367:l6744
  - Review and network meta-analysis of all available randomised trials that assessed prevention of gastrointestinal bleeding in critically ill patients
- MAGICapp (https://app.magicapp.org/public/guideline/j96g2L)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

units of blood, significant decrease in haemoglobin level, evidence of bleeding on upper gastrointestinal endoscopy, or need for surgery to control bleeding. When extracting data on overt bleeding, we included clinically important gastrointestinal bleeding. We accepted the definitions of pneumonia and *C difficile* infection used in each trial.

Data extraction

For each eligible study, two reviewers independently abstracted the following items with adjudication by a third reviewer: study characteristics (year of publication and country); population characteristics (sample size, age, proportion of males, type of intensive care unit, risk factors for gastrointestinal bleeding, and proportion of mechanical ventilation and enteral nutrition); description of interventions and comparators (the name, dose, administration route, frequency, and duration); and outcomes and their definitions.

Risk of bias assessment

Two reviewers independently assessed risk of bias with adjudication by a third reviewer, using a modified Cochrane Collaboration tool (Guyatt and Busse, modification of Cochrane tool to assess risk of bias in randomised trials) that includes sequence generation, allocation sequence concealment, blinding, missing outcome data (we judged high risk of bias if the rate of missing data was more than 5%), and other bias (in this case, early trial discontinuation due to benefit). Each criterion was judged as definitely or probably satisfied (low risk of bias), or probably or definitely not satisfied (high risk of bias). We did not summarise the overall risk of bias for studies across criteria.

Data synthesis and analysis

For each direct comparison for each outcome, we performed a Bayesian random-effects pairwise meta-analysis assessing heterogeneity with visual inspection of forest plots and the I^2 statistic.[19] We calculated odds ratios and corresponding 95% credible intervals (the Bayesian equivalent of frequentist confidence intervals) for all dichotomous outcomes, and mean differences with corresponding 95% credible intervals for continuous outcomes. We performed Egger test to assess the publication bias when 10 or more studies were available for a comparison.[20]

We performed a Bayesian random-effects network meta-analysis using Markov-chain Monte-Carlo simulation.[21 22] We used three chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. We assessed the convergence based on trace plots and the Brooks-Gelman-Rubin statistic, with an acceptable threshold of <1.05 for all nodes. We used non-informative priors for all parameters and assumed a common heterogeneity parameter for all treatment comparisons. We calculated the odds ratios and corresponding 95% credible intervals of network estimates with a consistency model. For all dichotomous outcomes, we calculated the absolute treatment effects of the network estimates based on the odds ratios and the event rates in the placebo arm in SUP-ICU trial using the modified Dias model, incorporating lines into the model.[23] The guideline panel searched for evidence on risk factors for bleeding and proposed four categories of risk of bleeding (linked *BMJ* Rapid Recommendation shows details on calculating baseline risks) and calculated absolute effects for each category for both clinically important gastrointestinal bleeding and overt bleeding. For continuous variables, when absent in reports, we estimated standard deviations from standard errors, P values, ranges, or interquartile ranges or, if none of these options was available, from other studies included in our network meta-analysis using a linear regression approach.[24]

For each paired comparison, we used conventional pairwise random-effects meta-analysis to inform the direct estimates and, through a node-splitting method, obtained the indirect estimates. We evaluated the ranking probabilities and calculated surface under the cumulative ranking curves (SUCRA). We used the node-splitting method to assess local incoherence (incoherence was assessed using both this test and the difference in point estimates and overlap of the credible intervals).[25] We assessed the incoherence of the entire network using global I^2 statistics. A comparison-adjusted funnel plot of treatment estimates addressed small-study effects.[26]

We conducted meta-regression to explore the impact of studies with high versus low risk of bias for each risk of bias criterion. For the network meta-regression, the no treatment or placebo group was the referent, and we assumed that effect modification differed between comparisons. If risk of bias influenced results, we included only low risk of bias studies in generating best estimates. To explore the impact of enteral nutrition and mechanical ventilation, we conducted meta-regression using the proportion of patients with enteral nutrition or mechanical ventilation as the independent variable. We performed subgroup analysis comparing results in studies that specified inclusion of critically ill patients with risk factors for gastrointestinal bleeding versus studies that did not mention risk factors in their inclusion criteria.

When networks are sparse, random-effects models may generate implausibly wide credible intervals from network meta-analysis estimates, even when the direct and indirect estimates are coherent. When this occurred, we either conducted a fixed-effect network meta-analysis or used the direct estimates as our best estimates of the treatment effects.[27 28] All network meta-analyses were performed using the *gemtc* package of *R* version 3.4.3 (R Core Team, Vienna, Austria), absolute effects in networks were calculated using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK), and *networkplot* command of Stata version 15.1 (StataCorp, College Station, Texas, USA) was used to draw the network plots.[29]

In networks with incoherence in many comparisons, we compared network estimates to direct and indirect

estimates. When we found direct versus network estimates inconsistent and counterintuitive, we examined odds ratios and relative risks in both random-effects and fixed-effect models, seeking an approach that provided plausible network estimates. When none of these approaches was satisfactory, we did not consider the network meta-analysis further for those outcomes and instead relied on direct paired comparisons as the best estimates of effect.

Assessment of certainty of evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach informed the assessment of certainty of evidence for each outcome (box 2),[31-33] including certainty ratings from the direct comparisons in our pairwise meta-analyses,[30 34-38] and certainty of evidence in network meta-analyses.[31 33] Certainty ratings of indirect estimates started at the lowest ratings of the direct comparisons that contributed to the most-dominant first order loop with further rating down, when necessary, for intransitivity. Ratings of the certainty of estimates for direct and indirect estimates to inform the rating of network estimates included risk of bias, inconsistency, indirectness and publication bias, while imprecision was assessed at the network level. We judged imprecision by comparing the confidence intervals or credible intervals to decision thresholds[34] chosen by the guideline panel. For the certainty of network estimates, we started with the estimate—direct or indirect—that dominated the network estimate, or used the higher of the direct and indirect estimates if they both contributed importantly to the network estimate. If incoherence was present, we rated down the certainty of the network estimates and used the estimate—direct or indirect—with the higher certainty evidence as the best estimate of treatment effect. We used the MAGICapp platform to develop the GRADE summary of finding tables.

Results

Description of included studies

Figure 1 shows the details of study selection process. We identified 479 records from our updated literature search and 13 potentially eligible studies from relevant reviews. After title and abstract screening, we assessed 70 full text articles, of which 18 proved eligible. Including 54 trials from our previous network meta-analysis (populations from three trials identified from previous network meta-analysis did not meet our eligibility criteria), we ultimately included 72 trials.

These 72 randomised controlled trials, with sample sizes from 22 to 3298, enrolled a total of 12 660 patients. Figure 2 presents the network plot including all outcomes and demonstrates that the most common comparisons were between H2RAs and placebo or no prophylaxis, followed by H2RAs versus sucralfate and PPIs versus H2RAs.

Fifty trials included critically ill patients with risk factors for gastrointestinal bleeding (appendix 2 summarises the risk factors listed), and 22 trials specified inclusion only of critically ill patients. Sixty five trials included patients in intensive care, two trials were of neurosurgery patients, one trial was of patients with fulminant hepatic failure, one trial of patients from three wards (department of intensive care, neurosurgery, and plastic surgery), and three trials of critically ill patients without further specification (appendix 3).

Risk of bias

Appendix 4 summarises risk of bias assessment that identified the main limitations as possible lack of allocation sequence concealment (54.2%), lack of blinding (62.5%), and excessive loss to follow-up (23.6%).

Outcomes

Appendix 5 presents network plots for each outcome. Tests of incoherence raised no concerns for mortality, pneumonia, *C difficile* infection, length of intensive care stay, length of hospital stay, and duration of mechanical ventilation. For clinically important gastrointestinal bleeding and overt bleeding, we found incoherence for comparisons of drugs with one another and no treatment and found counterintuitive results in each of the models we explored (appendix 6). Counterintuitive results included credible intervals for direct estimates from the network far (and implausibly) wider than confidence intervals for the direct estimates from the conventional paired meta-analysis; credible intervals for network estimates far and implausibly wider than the credible intervals for the direct comparisons; and network point estimates not being between the direct and indirect estimates. We therefore focused on results from direct pairwise meta-analysis rather than from network meta-analysis for clinically important gastrointestinal bleeding and overt bleeding, but used network meta-analysis results for all other outcomes. Appendix 7 presents SUCRA ranking of interventions for each outcome.

Mortality

Network meta-analysis estimates from 51 trials including 10 277 patients[11 12 14 39-87] demonstrated odds ratios for all comparisons close to 1.0 with moderate or very low certainty (table 1 of appendix 8). PPIs probably have no impact on mortality compared with placebo or no prophylaxis (odds ratio 1.06 (95% credible interval 0.90 to 1.28), 13 more per 1000

Box 2: Certainty of evidence and definitions[30]

- High certainty—We are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty—We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty—Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
- Very low certainty—We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

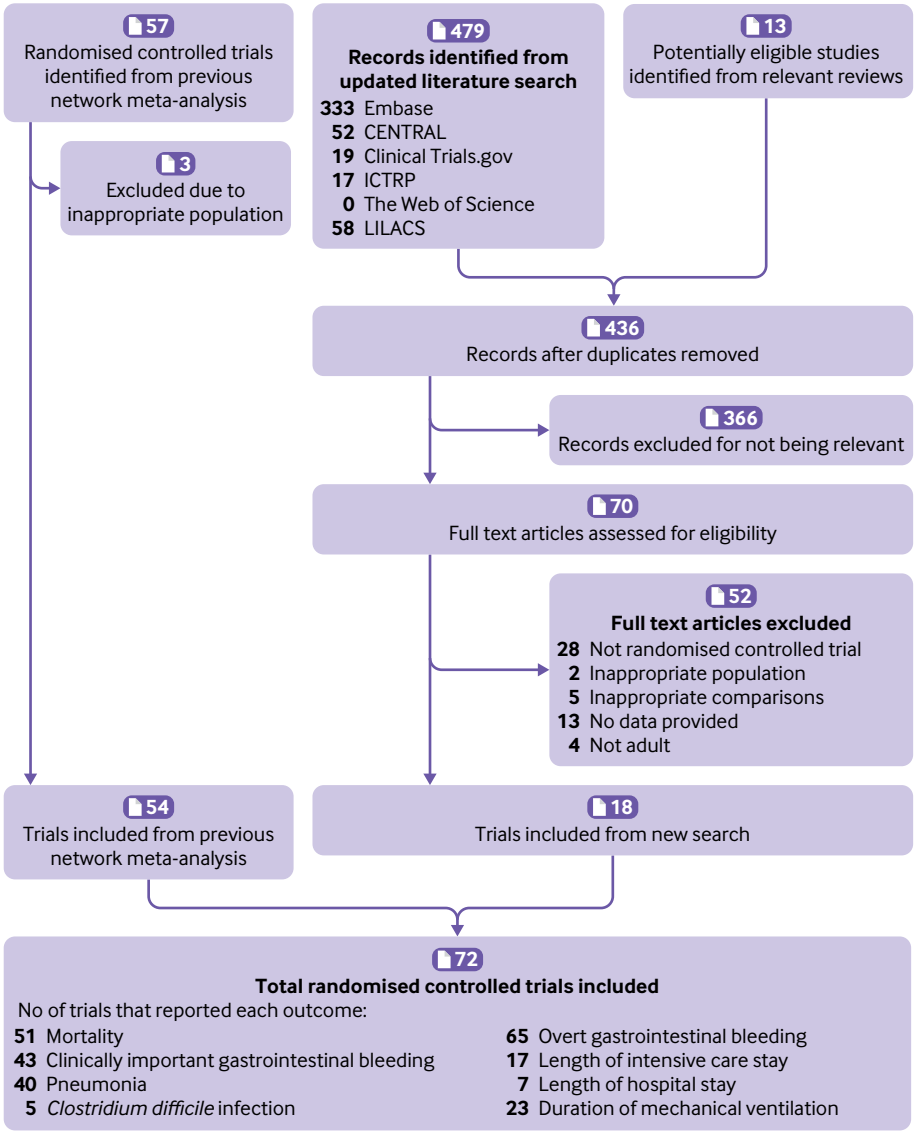

Fig 1 | PRISMA flow diagram of studies included in review of gastrointestinal bleeding prophylaxis

patients, moderate certainty, table 1 of appendix 8), and neither do H2RAs (0.96 (0.79 to 1.19), 9 fewer per 1000 patients, moderate certainty, table 1 of appendix 8). Network meta-regression suggested similar results in high and low risk of bias studies for mortality, and we therefore present results for all trials (appendix 9). The SUP-ICU trial reported a possible subgroup effect suggesting that PPIs relative to placebo may increase mortality in the sickest patients,[14] but the credibility of this subgroup effect is low (most important reasons for low credibility: the subgroup hypothesis and the direction of the subgroup effect are not specified a priori).[88]

Clinically important gastrointestinal bleeding

Forty three trials including 10 096 patients[11-14 41 44-47 49 52-58 60 61 63-65 67 69 73 74 76 78-83 85-87 89-96] reported clinically important gastrointestinal bleeding. Subgroup analysis based on each risk of bias criterion (concealment and blinding were highly correlated, so they were combined into one variable) showed that studies that failed to conceal or blind reported larger effect for PPIs versus H2RAs and smaller effect for H2RAs versus sucralfate (table 1 and appendix 10); for these comparisons, we focused on low risk of bias results.

We grouped patients into four categories according to risk of clinically important gastrointestinal bleeding: low risk (<2%), moderate risk (2-4%), high risk (>4-8%), and highest risk (>8%) (appendix 11), and calculated absolute effects for each category for clinically important gastrointestinal bleeding and overt bleeding.

Results demonstrated that, for patients at highest or high risk of bleeding, both PPIs and H2RAs probably reduce the risk of clinically important gastrointestinal bleeding compared with placebo or no prophylaxis. For PPIs the odds ratio was 0.61 (95% confidence interval 0.42 to 0.89), 33 fewer per 1000 for highest risk and 23 fewer for high risk patients, moderate certainty (table 2 and fig 3). For H2RAs the odds ratio was 0.46 (0.27 to

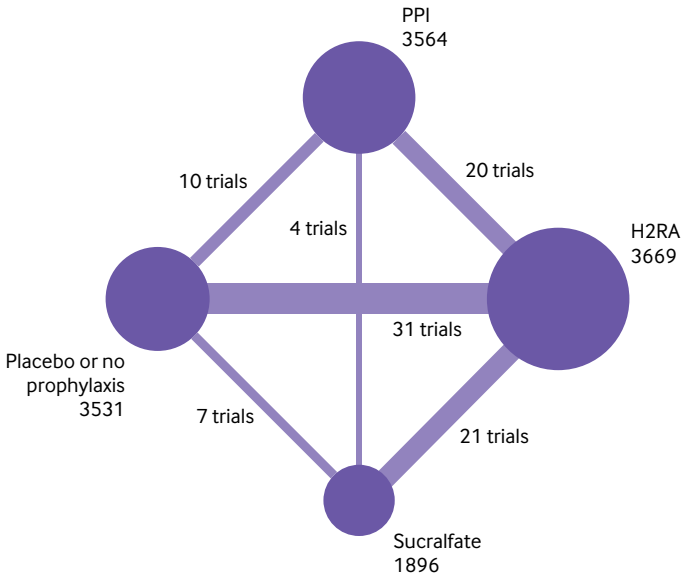

Fig 2 | Network plot of comparisons among proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, or no gastrointestinal bleeding prophylaxis

0.79), 46 fewer per 1000 for highest risk and 31 fewer for high risk patients, moderate certainty (table 2 and fig 4). For patients at lower risk, the absolute effects were considerably smaller (table 2). PPIs possibly reduce clinically important gastrointestinal bleeding relative to H2RAs, but the confidence intervals were wide and included a benefit of H2RAs (odds ratio 0.58 (0.29 to 1.17), table 2 and fig 5). H2RAs compared with sucralfate probably reduce clinically important gastrointestinal bleeding (odds ratio 0.46 (0.23 to 0.91), moderate certainty for higher risk groups, table 2). Evidence regarding sucralfate versus PPIs and placebo was essentially uninformative with very wide confidence intervals (table 2). Both subgroup analysis within the SUP-ICU trial and between trials meta-regression provided no support for the hypothesis that enteral nutrition influenced the relative impact of interventions (appendix 9 presents results for meta-regression and subgroup analysis).

Pneumonia

Forty trials including 9288 patients[11 14 39-41 44-48 53 54-56 57 59 61 63-67 69 71 73 75 76 79-83 85 90-95 97-99] reported pneumonia. PPIs may increase the risk of pneumonia compared with placebo or no prophylaxis (odds ratio 1.39 (95% credible interval 0.98 to 2.10), 50 more per 1000 patients, low certainty, table 3), as may H2RAs (1.26 (0.89 to 1.85), 34 more per 1000 patients, low certainty, table 3). PPIs may increase the risk of pneumonia compared with sucralfate (1.63 (1.12 to 2.46), 70 more per 1000 patients, low certainty, table 3), as may H2RAs (1.47 (1.11 to 2.03), 53 more per 1000 patients, low certainty, table 3). Network meta-regression suggested similar results in high and low risk of bias studies for pneumonia (appendix 9).

Table 1 | Low risk versus high risk of bias results (odds ratios (95% confidence intervals)) for clinically important gastrointestinal bleeding for different comparisons of gastrointestinal bleeding prophylaxis

Comparison	Low risk of bias result	High risk of bias result*	Subgroup difference (P value)
PPIs *v* placebo	0.62 (0.42 to 0.90)	0.33 (0.01 to 8.21)	0.70
H2RAs *v* placebo	0.43 (0.18 to 1.01)	0.54 (0.26 to 1.10)	0.69
Sucralfate *v* placebo	3.36 (0.34 to 33.13)	0.63 (0.28 to 1.41)	0.18
PPIs *v* H2RAs	0.58 (0.29 to 1.17)	0.20 (0.07 to 0.54)	0.08†
PPIs *v* sucralfate	0.31 (0.03 to 3.05)	0.27 (0.01 to 6.93)	0.95
H2RAs *v* sucralfate	0.46 (0.23 to 0.91)	1.18 (0.66 to 2.14)	0.04†

PPIs = proton pump inhibitors; H2RAs = histamine-2 receptor antagonists.
*Studies were at high risk of bias if either allocation sequence concealment or blinding were at high risk of bias.
†Important difference between low and high risk of bias result, so we used low risk of bias result as best estimate.

Clostridium difficile infection

Five trials including 3849 patients[11 12 14 80 96] reported *C difficile* infection, of which four compared PPI with placebo or no prophylaxis and one compared PPI with H2RA. *C difficile* infection was rare (baseline risk of 1.5%), and the absolute effect of any intervention would therefore be very small (for example, for PPIs versus placebo the odds ratio was 0.82 (95% credible interval 0.31 to 2.47), 3 fewer per 1000 patients, moderate certainty, see table 2 of appendix 8). Credible intervals around odds ratios were very wide, and results were therefore essentially uninformative (table 2 of appendix 8). Network meta-regression suggested similar results in high and low risk of bias studies for *C difficile* infection (appendix 9).

Overt gastrointestinal bleeding

Overt gastrointestinal bleeding is bleeding without the consequences of clinically important gastrointestinal bleeding such as haemodynamic changes, transfusion, haemoglobin decrease, or need for surgery. Sixty five trials including 11 662 patients[11-14 39 41-50 52-58 60-69 71-83 85-87 89-96 98-107] reported on overt bleeding. Subgroup analysis showed that concealment or blinding (the combined variable) influenced results for the comparisons of PPIs versus placebo and H2RAs versus sucralfate, and missing outcome data influenced results for PPIs versus placebo (table 4 and appendix 10). We therefore used low risk of bias results for these two comparisons. PPIs reduce overt bleeding relative to placebo (odds ratio 0.59 (95% confidence interval 0.45 to 0.76), high certainty, table 3 of appendix 8). This is probably also true for H2RAs versus placebo (odds ratio 0.38, (0.24 to 0.59), moderate certainty, table 3 of appendix 8). Sucralfate possibly reduces overt bleeding relative to placebo, but the confidence interval includes increased bleeding (odds ratio 0.58 (0.30 to 1.11), moderate certainty, table 3 of appendix 8). PPIs reduce overt bleeding relative to H2RAs (odds ratio 0.43 (0.25 to 0.74), high certainty, table 3 of appendix 8).

Meta-regression suggested the possibility that H2RAs versus placebo had a smaller relative effect when patients received enteral nutrition, but the credibility of this subgroup effect is low (most important reason for low credibility: the effect is suggested by comparisons between studies) (appendix 9).[88] Similarly, subgroup analysis suggested the

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Table 2 | GRADE summary of findings for clinically important gastrointestinal bleeding (CIB) for different comparisons of gastrointestinal bleeding prophylaxis

Comparison	Odds ratio (95% CI) and measurements	Absolute effect estimates (per 1000)			Absolute difference (95% CI) per 1000	Certainty in effect estimates	Plain text summary
PPIs *v* placebo	0.61 (0.42 to 0.89). 4317 patients in 8 studies	Low risk	Placebo: 12	PPIs: 7	−5 (−7 to −1)	Moderate*	PPIs probably reduce CIB by less than the amount most people would need to choose a PPI
		Moderate risk	30	19	−11 (−17 to −3)	Low*†	PPIs may reduce CIB by less than the amount most people would need to choose a PPI
		High risk	60	37	−23 (−34 to −6)	Moderate†	PPIs probably reduce CIB
		Highest risk	90	57	−33 (−50 to −9)	Moderate†	PPIs probably reduce CIB
H2RAs *v* placebo	0.46 (0.27 to 0.79). 1242 patients in 14 studies	Low risk	Placebo: 12	H2RAs: 6	−6 (−9 to −2)	Moderate*	H2RAs probably reduce CIB by less than the amount most people would need to choose a H2RA
		Moderate risk	30	14	−16 (−22 to −6)	Low*†	H2RAs may reduce CIB by less than the amount most people would need to choose a H2RA
		High risk	60	29	−31 (−43 to −12)	Moderate†	H2RAs probably reduce CIB
		Highest risk	90	44	−46 (−64 to −18)	Moderate†	H2RAs probably reduce CIB
Sucralfate *v* placebo	0.76 (0.36 to 1.62). 874 patients in 6 studies	Low risk	Placebo: 12	Suc: 9	−3 (−8 to 7)	Moderate*	Sucralfate probably does not have an important effect
		Moderate risk	30	23	−7 (−19 to 18)	Low*†	Sucralfate may not have an important effect
		High risk	60	46	−14 (−38 to 34)	Low‡	Sucralfate may not have an important effect
		Highest risk	90	70	−20 (−56 to 48)	Low‡	Sucralfate may not have an important effect
PPIs *v* H2RAs	0.58 (0.29 to 1.17). 1010 patients in 5 studies with low risk of bias	Low risk	H2RAs: 12	PPIs: 7§	−5 (−17 to 1)	Low*†	There may be no important difference
		Moderate risk	32	19§	−13 (−44 to 3)	Low*†	PPIs may reduce CIB more than H2RAs
		High risk	62	37§	−25 (−80 to 5)	Moderate†	PPIs probably reduce CIB more than H2RAs
		Highest risk	94	57§	−37 (−116 to 8)	Moderate†	PPIs probably reduce CIB more than H2RAs
PPIs *v* sucralfate	0.30 (0.05 to 1.92). 211 patients in 2 studies	Low risk	Suc: 23	PPIs: 7§	−16 (−117 to 3)	Very low*‡	Whether there is an important difference or not is very uncertain
		Moderate risk	61	19§	−42 (−260 to 9)	Very low*‡	Whether there is an important difference or not is very uncertain
		High risk	113	37§	−76 (−398 to 17)	Low‡	PPIs may reduce CIB compared with sucralfate
		Highest risk	168	57§	−111 (−490 to 27)	Low‡	PPIs may reduce CIB compared with sucralfate
H2RAs *v* sucralfate	0.46 (0.23 to 0.91). 1340 patients in 2 studies with low risk of bias	Low risk	Suc: 13	H2RAs: 6¶	−7 (−20 to −1)	Low*†	There may be no important difference
		Moderate risk	30	14¶	−16 (−44 to −1)	Low*†	H2RAs may reduce CIB compared with sucralfate
		High risk	61	29¶	−32 (−86 to −3)	Moderate†	H2RAs probably reduce CIB compared with sucralfate
		Highest risk	91	44¶	−47 (−123 to −4)	Moderate†	H2RAs probably reduce CIB compared with sucralfate

PPIs=proton pump inhibitors; H2RAs=histamine-2 receptor antagonists.
*Rated down due to uncertainty in baseline risk for some risk factors.
†Rated down for imprecision.
‡Rated down 2 levels for imprecision.
§We used the point estimate of absolute effect for PPIs, obtained from PPIs *v* placebo, to calculate absolute effect for PPIs *v* H2RAs and PPIs *v* sucralfate.
¶We used the point estimate of absolute effect for H2RAs, obtained from H2RAs *v* placebo, to calculate absolute effect for H2RAs *v* sucralfate.

possibility that PPIs versus placebo had a smaller effect in studies that specified that patient had risk factors for bleeding than those that did not mention risk factors in their inclusion criteria, but once again the credibility of this subgroup effect is low (most important reasons for low credibility: the effect is suggested by comparisons

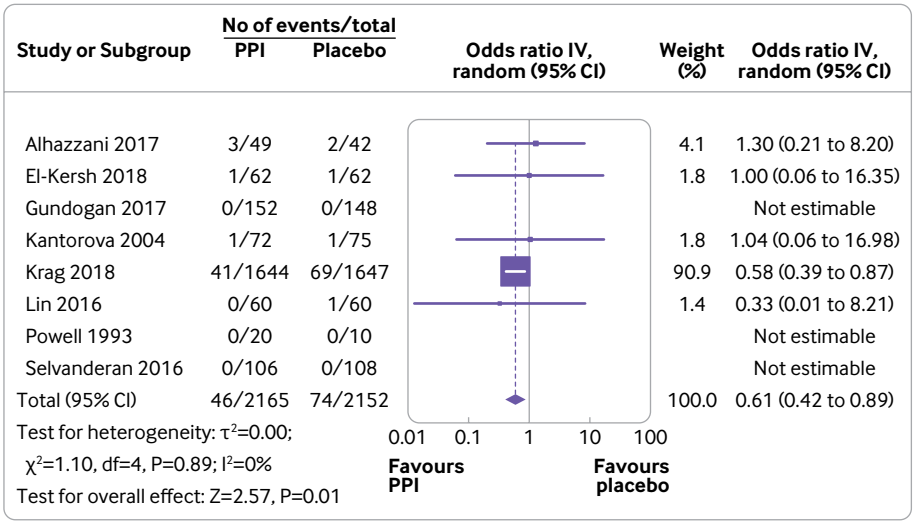

Fig 3 | Forest plot for proton pump inhibitors (PPIs) versus placebo for clinically important gastrointestinal bleeding

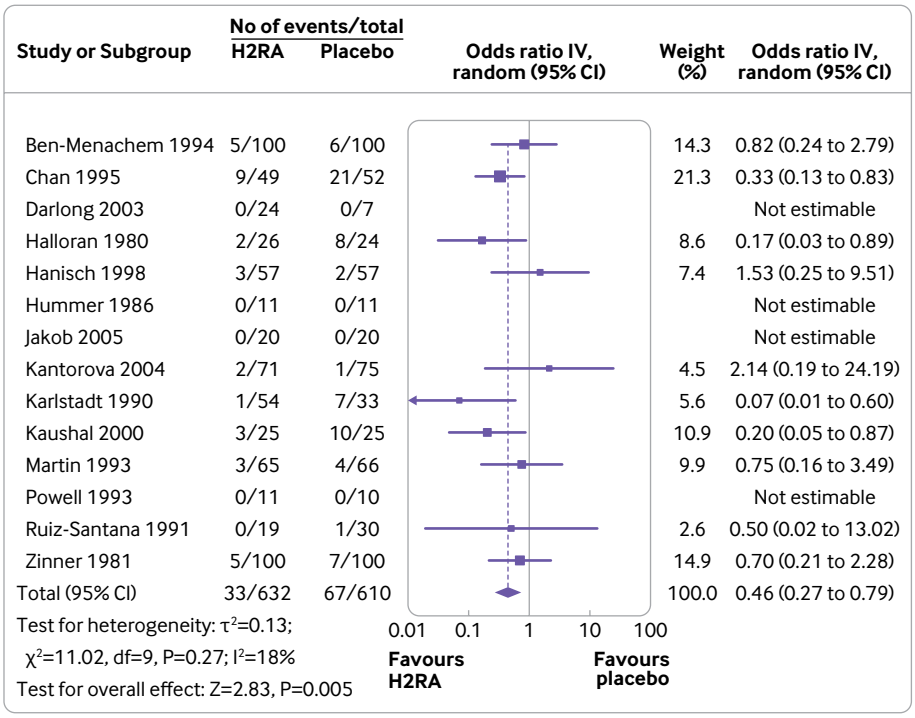

Fig 4 | Forest plot for histamine-2 receptor antagonists (H2RAs) versus placebo for clinically important gastrointestinal bleeding

between studies, and the subgroup hypothesis and the direction of the subgroup effect are not specified a priori) (appendix 9).[88]

Length of intensive care stay and length of hospital stay

Seventeen trials including 3533 patients[11 12 46 47 51 56 60 63 64 71 73 77 80-82 87 90 96] reported length of stay in intensive care, and seven trials including 831 patients[11 12 40 59 73 80 95] reported length of hospital stay. Results suggested no important difference between any of interventions (tables 4 and 5 of appendix 8). Network meta-regression suggested similar results in high and low risk of bias studies on results (appendix 9).

Duration of mechanical ventilation

Twenty three trials including 3625 patients[11 12 39-41 43 46 53 54 56 59 61 64 65 71 73 78 79 81 82 85 91 95 96] reported duration of mechanical ventilation or duration of intubation. Results suggested no important difference between any of interventions in terms of duration of mechanical ventilation or duration of intubation (table 6 of appendix 8). Network meta-regression suggested similar results in high and low risk of bias studies for duration of mechanical ventilation (appendix 9).

Discussion

We found moderate certainty evidence that neither PPIs nor H2RAs affect mortality compared with no prophylaxis (table 1 of appendix 8). We found lower

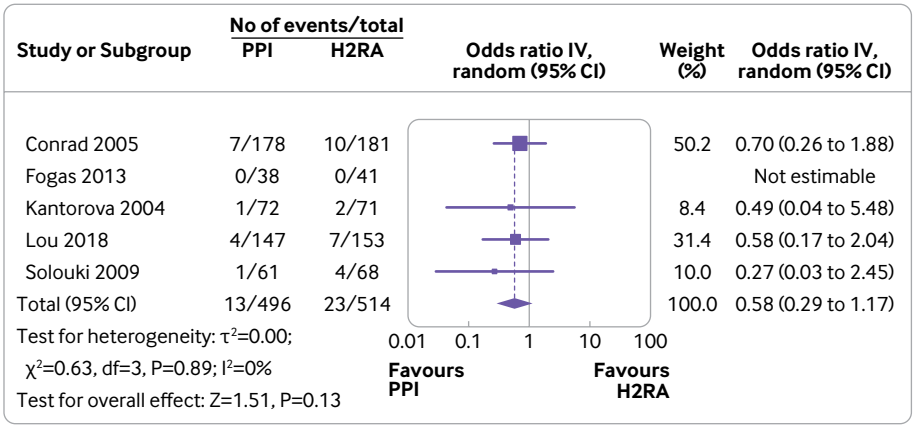

Fig 5 | Forest plot for proton pump inhibitors (PPIs) versus histamine-2 receptor antagonists (H2RAs) for clinically important gastrointestinal bleeding with low risk of bias studies

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Table 3 | GRADE summary of findings for pneumonia for different comparisons

Comparison	Direct estimate (95% CrI); Certainty of evidence	Indirect estimate (95% CrI); Certainty of evidence	Network estimate (95% CrI); Certainty of evidence*	Absolute effect estimates† (95% CrI) per 1000	
PPIs *v* placebo	1.08 (0.77 to 1.74); Moderate‡	1.78 (0.98 to 3.23); Moderate‡	1.39 (0.98 to 2.10); Low‡§¶	Placebo: 162	PPIs: 212 (159 to 287)
				Difference: 50 (−3 to 125)	
H2RAs *v* placebo	1.32 (0.87 to 2.02); Moderate‡	0.91 (0.50 to 1.94); Moderate‡	1.26 (0.89 to 1.85); Low‡§¶	Placebo: 162	H2RAs: 196 (148 to 263)
				Difference: 34 (−14 to 101)	
Sucralfate *v* placebo	2.13 (0.69 to 6.74); Moderate‡	0.68 (0.42 to 1.11); Moderate‡	0.85 (0.56 to 1.33); Low‡§	Placebo: 162	Sucralfate: 142 (98 to 204)
				Difference: −20 (−64 to 42)	
PPIs *v* H2RAs	1.10 (0.79 to 1.51); Moderate‡	1.03 (0.57 to 1.95); Moderate‡	1.11 (0.82 to 1.50); Low‡§	H2RAs: 196 (148 to 263)	PPIs: 212 (159 to 287)
				Difference: 16 (−32 to 68)	
PPIs *v* sucralfate	2.89 (1.38 to 6.00); Moderate‡	1.27 (0.84 to 2.04); Moderate‡	1.63 (1.12 to 2.46); Low‡§	Sucralfate: 142 (98 to 204)	PPIs: 212 (159 to 287)
				Difference: 70 (18 to 131)	
H2RAs *v* sucralfate	1.34 (1.04 to 1.82); Moderate‡	2.77 (0.90 to 8.24); Moderate‡	1.47 (1.11 to 2.03); Low‡§	Sucralfate: 142 (98 to 204)	H2RAs: 196 (148 to 263)
				Difference: 53 (15 to 99)	

CrI = credible interval; PPIs = proton pump inhibitors; H2RAs = histamine-2 receptor antagonists.
*Higher of direct or indirect confidence (without consider imprecision), and then considered imprecision and incoherence.
†We used as baseline risk in the placebo group of the SUP-ICU trial.
‡Rated down for risk of bias.
§Rated down for imprecision.
¶We are skeptical of the result because the pooled result including smaller studies conflicts with the evidence from the largest study (SUP-ICU).

certainty evidence of no impact on mortality for other comparisons (table 1 of appendix 8).

We found moderate or low certainty evidence that PPIs and H2RAs probably reduce clinically important gastrointestinal bleeding relative to no prophylaxis (table 2) and high or moderate certainty evidence that both drugs reduce overt gastrointestinal bleeding relative to no prophylaxis (table 3 of appendix 8). For higher risk patients, the impact on clinically important gastrointestinal bleeding may be important (PPIs absolute difference for highest risk patients 3.3%, for high risk patients 2.3%; H2RAs for highest risk patients 4.6%, for high risk patients 3.1%; table 2); this may not be true for lower risk patients (table 2). PPIs relative to H2RAs possibly reduce clinically important gastrointestinal bleeding, but the confidence interval included superiority of H2RAs (odds ratio 0.58 (95% confidence interval 0.29 to 1.17), table 2 and fig 5). Sucralfate may not reduce clinically important gastrointestinal bleeding (table 2).

PPIs and H2RAs may increase the risk of pneumonia (absolute increases 5.0% and 3.4% respectively, table 3). *C difficile* infection occurred infrequently, resulting in very wide credible intervals around odds ratios that were essentially uninformative. However, because *C difficile* infection was rare, even the largest plausible increase in risk will be small. Few trials reported on other adverse effects. Prophylaxis may have no impact on length of intensive care stay, length of hospital stay, or duration of mechanical ventilation.

Strength and limitations of study

Strengths of this review include a comprehensive search to identify eligible trials; independent study selection, data extraction, and risk of bias assessment by two reviewers; focus on low risk of bias studies when low and high risk of bias studies yielded differing results; and application of the GRADE approach to rate the certainty of evidence. We also presented absolute effects for all comparisons and outcomes and for patients at different risk of gastrointestinal bleeding.

Finally, rather than mechanically reporting network meta-analysis results, we also considered whether they might be misleading. It is probably inadvisable to conduct network meta-analysis when direct and indirect estimates differ considerably throughout the network (that is, incoherence).[28] We found this problem for both clinically important gastrointestinal bleeding and overt bleeding and, probably as a result, found network meta-analysis estimates that were inconsistent with direct estimates and counterintuitive. Testing different measures of effect or model assumptions did not resolve the issue. Therefore, for these two outcomes, we relied on direct comparisons only.

Limitations include clinical heterogeneity across eligible trials that enrolled different populations and often did not clearly identify the risk factors for bleeding in the participating individuals. However, most patients in most trials received mechanical ventilation, an indication for prophylaxis in most intensive care units worldwide. Definitions of clinically important gastrointestinal bleeding and overt bleeding differed; most, however, adhered to standard criteria. Most trials did not report the duration of follow-up.

Some results proved logically inconsistent. For instance, in comparisons against placebo or no prophylaxis, results showed larger effects with H2RAs than with PPIs on reduction in clinically important gastrointestinal bleeding. Direct comparisons of the two agents, however, raised the possibility that PPIs result in larger reductions in clinically important gastrointestinal bleeding than do H2RAs.

Enteral nutrition may provide protection against gastrointestinal bleeding, and the impact of prophylaxis in patients receiving enteral nutrition may therefore be small, at least in patients at otherwise lower risk. It is also possible that enteral nutrition decreases the relative effect of prophylaxis on bleeding. Although meta-regression results suggested H2RAs had smaller relative effect on overt bleeding when patients received enteral nutrition, this subgroup effect proved of low credibility (appendix 9).[88] We also identified a possible

Table 4 | Low risk versus high risk of bias results (odds ratios (95% confidence intervals)) for overt gastrointestinal bleeding

Comparison	Low risk of bias result	High risk of bias result*	Subgroup difference (P value)
PPIs *v* placebo	0.59 (0.45 to 0.76)	0.20 (0.09 to 0.48)	0.02†
H2RAs *v* placebo	0.34 (0.19 to 0.61)	0.45 (0.23 to 0.88)	0.54
Sucralfate *v* placebo	3.36 (0.34 to 33.13)	0.52 (0.28 to 0.95)	0.12
PPIs *v* H2RAs	0.57 (0.27 to 1.23)	0.32 (0.16 to 0.65)	0.28
PPIs *v* sucralfate	0.31 (0.03 to 3.05)	0.11 (0.01 to 2.20)	0.59
H2RAs *v* sucralfate	0.46 (0.23 to 0.91)	1.47 (1.01 to 2.15)	0.004†

*For PPIs versus placebo, studies were at high risk of bias if either allocation sequence concealment or blinding or missing outcome data were at high risk of bias. For other comparisons, studies were at high risk of bias if either allocation sequence concealment or blinding were at high risk of bias.
†Important difference between low and high risk of bias result, so we used low risk of bias result as best estimate.

subgroup effect for PPIs versus no prophylaxis: studies in which investigators specified that patients had risk factors had apparently smaller effects on overt bleeding than those in which there was no mention of risk factors. Once again, however, the apparent subgroup effect is of low credibility (appendix 9).[88]

Relation to prior work

Compared with previous, conventional pairwise meta-analysis, the use of indirect comparisons within this network meta-analysis adds additional information to the evidence regarding gastrointestinal bleeding prophylaxis, particularly with respect to establishing the impact of PPIs on gastrointestinal bleeding. Our review included more trials and substantially more patients: most importantly the SUP-ICU trial,[14] which is both the largest trial to date addressing prophylaxis and at low risk of bias (the SUP-ICU trial concealed randomisation, blinded clinicians and study personnel, and lost very few patients to follow-up, and was thus at low risk of bias). In this review, we found that H2RAs likely reduce the risk of clinically important gastrointestinal bleeding compared with no prophylaxis and sucralfate; our previous network meta-analysis suggested no convincing impact of H2RAs. One consequence of this review's focus on studies at low risk of bias when results differed in high risk and low risk of bias studies was a confidence interval for the comparison of PPIs versus H2RAs on clinically important gastrointestinal bleeding wider than those in previous studies and including the possibility of benefit with H2RAs.

We found moderate certainty evidence that neither PPIs nor H2RAs reduce mortality relative to no prophylaxis. The SUP-ICU trial reported a possible subgroup effect suggesting PPIs may increase mortality in the sickest patients. Applying suggested criteria, however, demonstrated this possible subgroup effect is of low credibility (appendix 9).[88]

Implications of study

This systematic review provides important information for weighing the potential benefits and harms of alternative interventions for gastrointestinal bleeding prophylaxis in adult critically ill patients. Key messages include the likelihood that no intervention influences mortality; that PPIs and H2RAs likely reduce bleeding; that reduction in bleeding is higher in patients with higher baseline risk of bleeding; and that resolving a number of issues, including the possibility that prophylactic agents increase the risk of pneumonia, will require additional randomised controlled trials. This review provides key evidence for the associated *BMJ* Rapid Recommendation, which uses additional context and methodology to produce recommendations for clinical practice.

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Contributors: GHG, ZY, YW, and LL conceived the study. KD and ZY designed the search strategy, and KD performed the literature search. YW and XW screened studies for eligibility. XW, YW, Yingkai Wang, and ZM performed data extraction. YW, ZY, and GHG assessed the risk of bias. LG, LH, and YW performed data analysis. YW, RAS, LG, ZY, and GHG interpreted the data analysis and assessed the certainty of evidence. YW, LG, and ZY wrote the first draft of the manuscript, and all other authors revised the manuscript. GHG and LL are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: No additional data available.

Transparency: The manuscript's guarantors (GHG and LL) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix 1: Search terms and strategies
Appendix 2: List of risk factors identified from included trials
Appendix 3: Study characteristics and outcome definition
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