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Pharmacological interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units: a network meta-analysis

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Abstract

Objectives To assess the efficacy and safety of pharmacological interventions for preventing upper gastrointestinal (GI) bleeding in people admitted to intensive care units (ICUs).

Design and setting Systematic review and frequentist network meta-analysis using standard methodological procedures as recommended by Cochrane for screening of records, data extraction and analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence.

Participants Randomised controlled trials involving patients admitted to ICUs for longer than 24 hours were included.

Search methods The Cochrane Gut Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and Latin American and Caribbean Health Science Information database (LILACS) databases were searched from August 2017 to March 2022. The search in MEDLINE was updated in April 2023. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Main outcome measures The primary outcome was the prevention of clinically important upper GI bleeding.

Results We included 123 studies with 46 996 participants. Cimetidine (relative risk (RR) 0.56, 95% CI 0.40 to 0.77, moderate certainty), ranitidine (RR 0.54, 95% CI 0.38 to 0.76, moderate certainty), antacids (RR 0.48, 95% CI 0.33 to 0.68, moderate certainty), sucralfate (RR 0.54, 95% CI 0.39 to 0.75, moderate certainty) and a combination of ranitidine and antacids (RR 0.13, 95% CI 0.03 to 0.62, moderate certainty) are likely effective in preventing upper GI bleeding. The effect of any intervention on the prevention of nosocomial pneumonia, all-cause mortality in the ICU or the hospital, duration of the stay in the ICU, duration of intubation and (serious) adverse events remains unclear.

Conclusions Several interventions seem effective in preventing clinically important upper GI bleeding while there is limited evidence for other outcomes. Patient-relevant benefits and harms need to be assessed under consideration of the patients' underlying conditions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients in intensive care unit are at risk of gastrointestinal (GI) bleeding and they receive acid suppressants. Published systematic reviews and meta-analyses on the pharmacological treatment for prevention of upper GI bleeding were restricted to a limited number of interventions.

⇒ Due to inclusion of a limited number of studies/interventions, evidence remains inconsistent and inconclusive.

WHAT THIS STUDY ADDS

⇒ This is an up-to-date network meta-analysis summarising all relevant evidence and presenting results using the Grading of Recommendations Assessment, Development and Evaluation approach.

⇒ In this network meta-analysis of 123 randomised trials and 46 996 patients, we found beneficial effect of several interventions (cimetidine, ranitidine, antacids, sucralfate and a combination of ranitidine and antacids) for the prevention of clinically important upper GI bleeding, compared with placebo.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Decisions about whether and which interventions are effective in participants at risk for upper GI bleeding should be made under consideration of their underlying condition, age and other risk factors and comorbidities.

Introduction

Critically ill patients are at risk of developing stress ulcers. A proportion of these patients develop clinically important gastrointestinal (GI) bleeding, and the mortality rate in such patients is high.[1 2] Numerous randomised controlled trials (RCTs) and non-randomised studies have investigated the role of different stress ulcer prophylactic drugs and strategies for the prevention of stress ulcers and thereby upper GI bleeding.[3–5] In pooled analysis, when compared with placebo, stress ulcer prophylaxis with antacids, H2 receptor antagonists (H2RAs) or sucralfate results in a reduction in clinically important bleeding with prophylaxis.[6–11] In a recent large RCT enrolling 3298 patients and comparing pantoprazole, a proton pump inhibitor (PPI), with placebo, there was no difference in the 90-day mortality despite a significant reduction (relative risk (RR) 0.58, 95% CI 0.40 to 0.86) in one or more episodes of clinically important GI bleeding.[12] Stress ulcer prophylaxis, on the other hand, also alters the acidity of the stomach content leading to changes in gastric and tracheobronchial colonisation with pathogenic bacteria. This may result in an increased risk for the development of ventilator-associated pneumonia, *Clostridium difficile* diarrhoea or other therapy-related adverse events. There is also evidence that the addition of pharmacological stress ulcer prophylaxis in enterally fed patients, does not result in a reduction in the incidence of GI bleeding when compared with patients who received enteral feeding alone.[13] Hence, prophylaxis may not be indicated in all critically ill patients[2 14] and is often overused. Thus, the benefits of stress ulcer prophylaxis need to be balanced against its risks.

Over the last few years, despite a growing number of systematic reviews that were conducted on the prevention of upper GI bleeding, systematic reviews and meta-analyses were narrowed to comparisons of a limited number of interventions. These have been inconclusive or generated conflicting results.[6 8 10 13 15–21] While there are new and ongoing studies on the topic[22], a network meta-analysis (NMA) of current evidence on different pharmacological interventions for prophylaxis of upper GI bleeding was undertaken to provide direct and indirect evidence on the benefits and harms of bleeding prophylaxis in patients admitted to the intensive care unit (ICU). The current study is an extension and update of our Cochrane review published in 2018, presents new findings derived from an NMA, offering additional depth for informed decision-making.[11]

Methods

We produced this NMA as an additional, updated analysis of our previously published Cochrane review[11] and followed the objectives described in the review protocol.[23] We reported this NMA in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) NMA reporting guideline[24] and conducted the systematic review according to Cochrane standards.[25] Refer to online supplemental file 1 for the PRISMA NMA checklist.

Eligibility criteria

All RCTs with participants (any age and gender) admitted to ICUs for longer than 24 hours were included. We excluded studies in which participants were admitted to the ICU primarily for management of upper GI bleeding. We compared the following interventions administered by any route and at any dose: H2RA, PPIs, prostaglandin analogues, anticholinergics, potassium-competitive acid blockers, systemic and non-systemic drugs that neutralise gastric acid (antacids), ulcer protectives, ulcer healing drugs and other pharmacological intervention used to reduce upper GI bleeding and combinations of interventions (eg, omeprazole-bicarbonate combinations). We compared each class of drugs versus placebo or no prophylaxis and we compared all classes of drugs against one another. We did not compare different drugs within a single class with one another.

Outcomes

Our primary outcome of interest was clinically important upper GI bleeding. For this outcome, we used the definition used by the study authors. Our secondary outcomes were nosocomial pneumonia including ventilator-associated pneumonia, all-cause mortality in ICU, all-cause mortality in the hospital, duration of intubation, including duration of mechanical ventilation, the number of participants requiring blood transfusions, the number of units of blood transfused, serious adverse events of interventions leading to discontinuation of treatment, prolongation of ICU stay or disability; any other adverse event and *C. difficile*-related diarrhoea.

Search methods

Information specialist (SS) updated the search strategy used in the previously published Cochrane Review[11] by adding relevant new indexing terms and text words, adjusting existing search strings, and removing redundant search terms. Cochrane Highly Sensitive Search Strategies were used for identifying randomised controlled trials and controlled clinical trials in Ovid MEDLINE and Ovid Embase (as described in Technical Supplement to Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions; minor revisions were made to Ovid MEDLINE filter).[26] The Controlled clinical trial filter incorporated into the database interface was applied in LILACS. The updated search strategy aimed to identify publications added to the databases and trials registries after the date of the searches in the Cochrane Review[11], which were conducted in August 2017. There were no language restrictions.

We searched the following databases on 25 May 2021 and then again on 1 March 2022 using search strategies provided in online supplemental file 2:

- Cochrane Gut Specialised Register.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 4 and CENTRAL; 2022, Issue 2) in the Cochrane Library.
- MEDLINE Ovid (1946 to 24 May 2021 and 1946 to 25 February 2022).
- Embase Ovid (1974 to 24 May 2021 and 1974 to 28 February 2022).
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 25 May 2021 and 1982 to 1 March 2022).

We searched the following trials registries on 25 May 2021 and then again on 1 March 2022 using search strategies reported in online supplemental file 2:

- ClinicalTrials.gov (https://clinicaltrials.gov).
- WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/).

We retrieved the bibliographies of included studies manually or through Web of Science Core Collections and Scopus and checked them for relevant trials. We updated the search in MEDLINE Ovid on 20 April 2023 (IT). The included studies were checked for any retraction, errata or corrections.

Data extraction and quality assessment

Two review authors from a pool of five (IT, LK, MTB, SH, MAW, JVP and JLZN) independently screened each title, abstract and

full text, extracted data in a standardised form and assessed them with the Cochrane Risk of Bias Tool. We resolved disagreements through discussion. We classified a study's overall risk of bias as high if the study had high risk of bias in any domain. Likewise, we classified the risk of bias as unclear if the study had no high risk of bias and had unclear risk of bias in any domain. Last, we classified a study's overall risk of bias as low if the study had low risk of bias in all domains.

Data synthesis

We used risk ratios for dichotomous outcomes and mean differences for continuous outcomes, with their respective 95% CIs. We assessed heterogeneity between studies by visually examining the forest plot to check for overlapping CIs and by using the χ^2 test for homogeneity with a 10% level of significance and the I^2 statistic. We assessed the likelihood of potential publication bias by using funnel plots, provided that at least 10 studies were included in a meta-analysis.

Firstly, we performed standard pairwise meta-analyses for every treatment comparison (not reported here) if adequate.[27] We combined continuous data using the weighted mean difference. We used the random-effects model for data synthesis when we identified heterogeneity as substantial or considerable based on χ^2 test and I^2 statistics. We interpreted I^2 values from 0% to 25% as possibly not important, from 26% to 50% as moderate heterogeneity, from 51% to 75% as substantial heterogeneity and from 76% to 100% as considerable heterogeneity.

We assessed the feasibility of conducting NMA by examining several key factors. These included (1) the abundance of available evidence, such as the number of trials and interventions (2); the consistency in study designs, participants, intervention characteristics and outcome definitions across the body of evidence, based on the transitivity assumption (the presence of bleeding disorders and definition of outcomes) (3) network connectivity and (4) the coherence or consistency within the network as a whole, as well as within each closed loop, using the 'design-by-treatment' model.

We conducted NMAs to compare multiple interventions simultaneously for each outcome. When two or more interventions were combined, we considered this as a separate intervention ('node'). We obtained a network plot or geometry plot to ensure that the trials were connected by interventions using Stata/SE V.15.1.[28] A geometric plot visually presents all available direct comparisons for each outcome. In this plot, each node represents a specific intervention. In network map, the size of the node (circle) corresponds to the number of patients randomised to that intervention. The thickness of the lines corresponds to the number of studies for each comparison. We excluded trials that were not connected to the network from the NMA and reported only the direct pairwise meta-analysis for such comparisons. We assumed a common estimate for the heterogeneity variance across all the different comparisons. The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter estimated from the multivariate meta-analysis. Issues of inconsistency were identified by comparing direct evidence with indirect evidence using the node-splitting method and assuming a common heterogeneity estimate within each loop.[29] Where we found important heterogeneity and/or inconsistency, we explored the possible sources for primary outcomes.

We performed random-effects NMA within a frequentist framework using a multivariate meta-analysis estimated by restricted maximum likelihood to assess the comparative effectiveness. We considered placebo and placebo/no prophylaxis under one intervention as placebo. We used 'placebo' as the reference group across the networks, as this was the most common intervention compared in the trials. We estimated ranking probabilities, the surface under the cumulative ranking curve and generated mean treatment rankings for each outcome. Network meta-regression was conducted to explore the impact of studies with the presence of bleeding disorders, pneumonia at the time of admission and others.

Subgroup and sensitivity analysis

Based on the data, we carried out the following subgroup analyses for each comparison.

- Presence or absence of bleeding disorders (eg, coagulopathies, defined as thrombocyte count <50/nL, partial thromboplastin time >2 times the upper limit of the normal range, international normalised ratio >1.5).
- Pneumonia at the time of ICU admission.
- Adults (≥18–65 years) versus older adults (≥65 years) versus children and adolescents (<18 years).

We conducted sensitivity analyses by:

- Evaluating studies with low risk of bias versus studies with high or unclear risk of bias.
- Drop-out rates of 10% or greater.

One review author assessed the certainty of the evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) domains for NMA and pairwise meta-analyses, respectively.[30] The assessment was checked by a second researcher. Any disagreements were resolved through discussion or by consultation with a third review author. We used a minimally contextualised approach to rank and present the studies according to effectiveness.[31]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Description of studies

We retrieved 4061 unique records through searching databases and other sources. We included in the review 142 records[3–5 12 32–168] reporting on 123 studies. Of 142 records, we identified 12 ongoing studies.[169–180] We excluded a total of 55 records (see online supplemental file 3). The process of study selection is described in figure 1. The 123 studies randomised a total of 46 996 participants to 24 comparisons involving 15 different treatment modalities. Most studies specifically mentioned that they randomised individuals who had no history of GI bleeding or peptic ulcer or gastritis or were not undergoing treatments for any of these conditions. The included studies included participants admitted to ICUs, although the level of ICUs into which participants were admitted was not always clearly mentioned. Among the included studies, 8 were exclusively paediatric studies[5 39 61 90 91 99 132 165]; and 11 studies reported as conference abstracts only.[65 67 80 95 102 103 113 127 130 141 162]

Information about the assessments of the risk of bias for all included studies is presented in figure 2.

Effects of interventions

See online supplemental file 4 for a summary of the effects of interventions on the main outcome of this review. Based on the available data, we produced nine different networks. Although not all the networks included all nodes, we defined separate nodes across this review: H2RAs, PPIs, sucralfate, antacids,

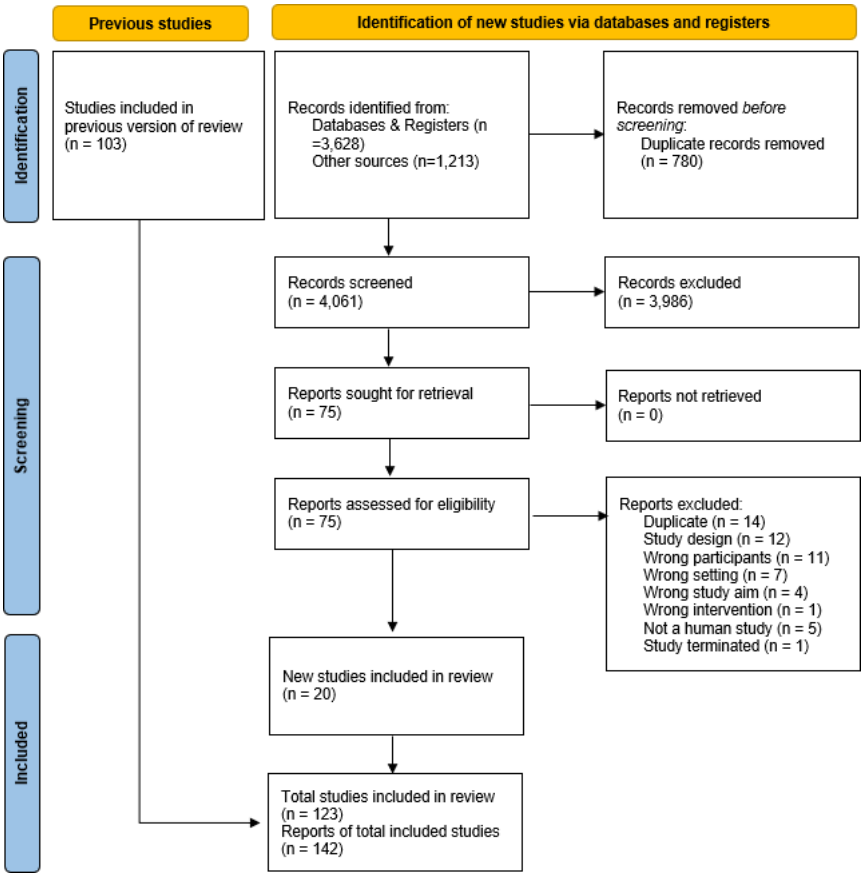

Figure 1 PRISMA flow diagram of included studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

bioflavonoids, anticholinergics (pirenzepine), prostaglandin analogues, teprenone, placebo or no prophylaxis.

During the feasibility assessment, we observed inconsistencies within the network, particularly stemming from the H2RAs and PPIs drug class. To address this issue, we disintegrated the H2RAs and PPIs based on the specific drugs involved, which effectively eliminates the inconsistency within the network.

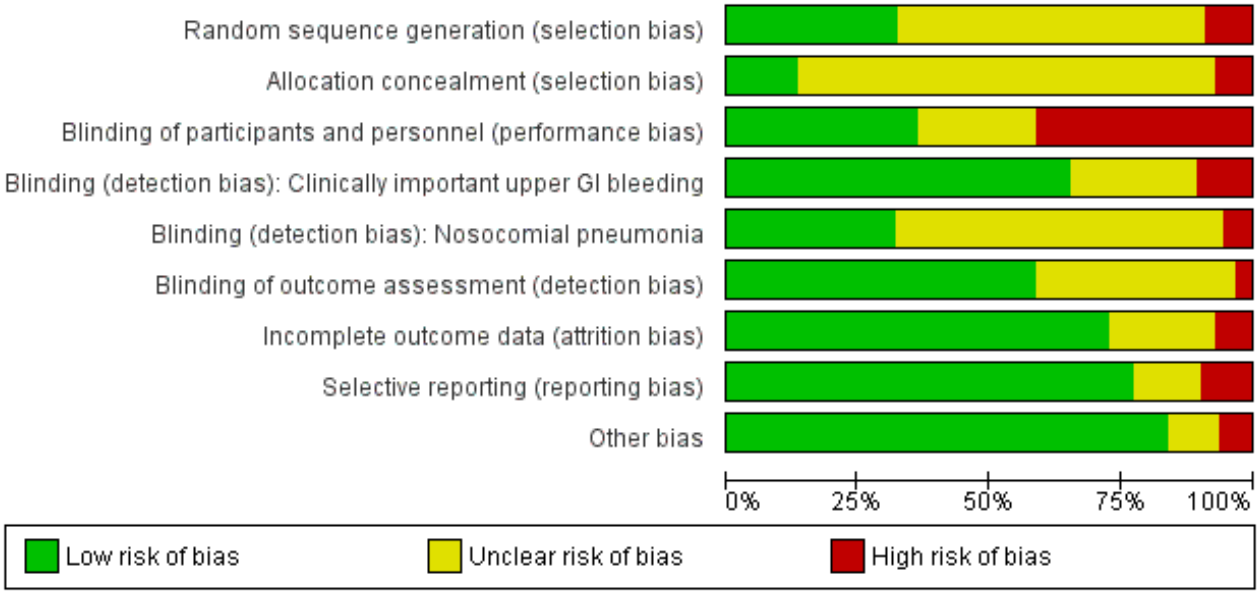

Figure 2 Risk of bias graph

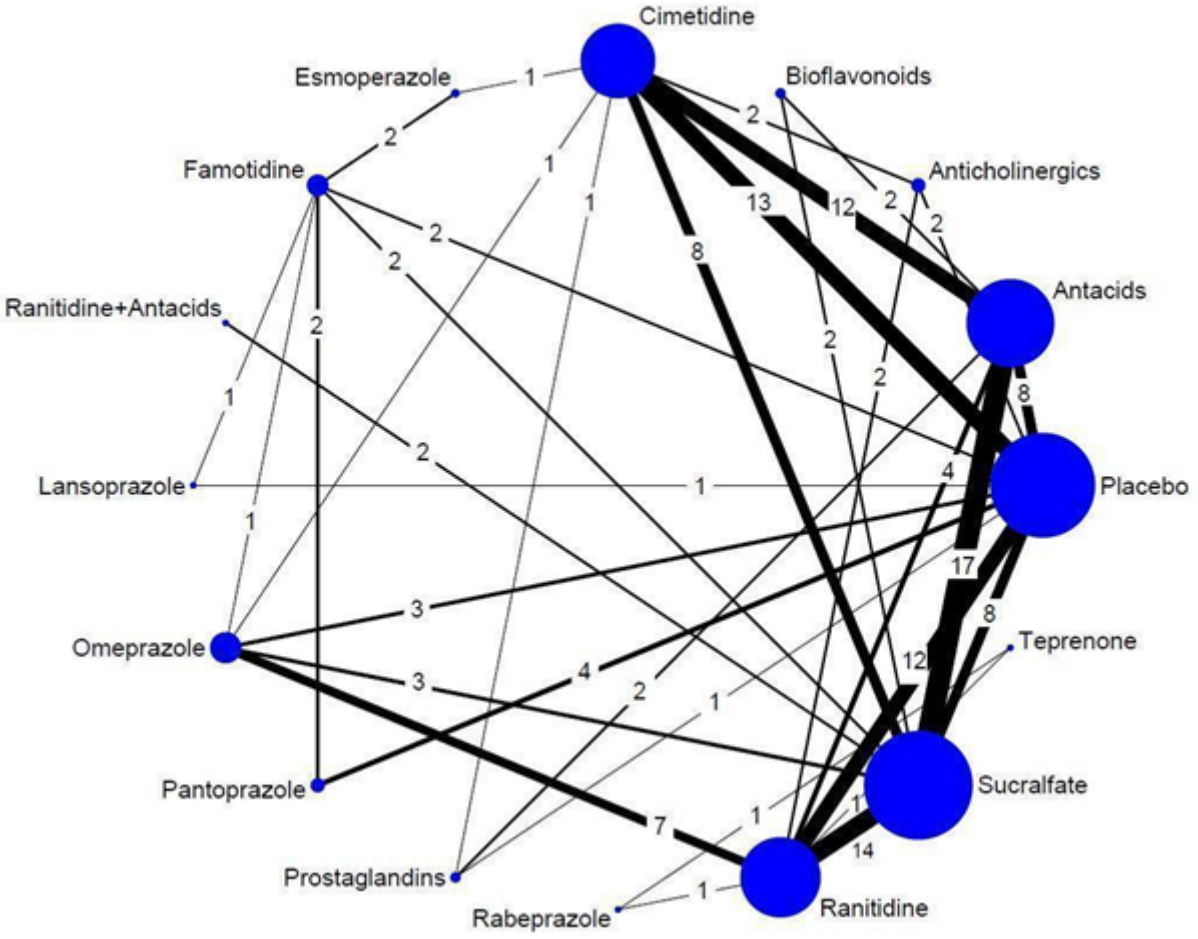

Figure 3 Network of interventions for gastrointestinal bleeding.

Primary outcome (clinically important upper GI bleeding)

We included 94 RCTs in the analysis with 42 548 participants (see figure 3). No evidence of global or loop-specific incoherence was found in the network (see online supplemental file 5).

Compared with placebo, ranitidine with antacids likely reduces clinically important upper GI bleeding (see table 1, RR 0.13, 95% CI 0.03 to 0.62, moderate certainty evidence). Also, cimetidine (RR 0.56, 95% CI 0.40 to 0.77, 13 studies, 1288 participants; 79 fewer cases per 1000 from 108 fewer to 41 fewer), ranitidine (RR 0.54, 95% CI 0.38 to 0.76, 12 studies, 871 participants; 88 fewer cases per 1000 (from 118 fewer to 46 fewer), antacids (RR 0.48, 95% CI 0.33 to 0.67, 8 studies, 708 participants; 87 fewer cases per 1000, from 113 fewer to 54 fewer) and sucralfate (RR 0.54, 95% CI 0.39 to 0.75, 8 studies, 698 participants; 58 fewer cases per 1000, from 78 fewer to 32 fewer) likely reduce clinically important upper GI bleeding compared with placebo (moderate certainty evidence) (see summary of findings in table 2). Omeprazole, lansoprazole, esomeprazole and pirenzepine might be more effective than placebo but the evidence is of low or very low certainty. There was no clear effect of other interventions on the incidence of clinically important upper GI bleeding. All effect estimates and rankings are reported in online supplemental file 6,7.

Secondary outcomes

For the secondary outcomes, no evidence of global or loop-specific incoherence was found in any of the networks (see online supplemental file 5). The certainty of the evidence varied between moderate and very low and there seem to be no clear effects on nosocomial pneumonia (46 RCTs with 10 341 participants, see summary of findings table in online supplemental file 4), all-cause mortality in the ICU (73 RCTs with 37 232 participants) (see online supplemental file 6), all-cause mortality in hospital (18 RCTs with 32 486 participants), duration of ICU stay, duration of intubation (20 RCTs with 3016 participants), serious adverse events (17 studies with 32 463 participants) or the incidence of C.difficile diarrhoea (8 studies with 31 003 participants).

Compared with placebo, antacid (RR 0.44, 95% CI 0.25 to 0.79, 2 studies and 226 participants, moderate certainty) was the most effective treatment for reducing the number of people that required blood transfusions (see summary of findings table in online supplemental file 4). Refer to online supplemental file 8 for all the network plots of secondary outcomes.

In pairwise meta-analyses, there seems to be no difference between H2RAs or sucralfate and placebo or no prophylaxis with respect to the number of units of blood transfused (MD 0.09 units, 95% CI −0.99 to 1.17, 3 studies, 309 participants, see online supplemental file 8).

For adverse events, only pairwise meta-analysis was performed because only a few comparisons included data about adverse events and the list of adverse events varied. There seems to be no clear difference in the risk for any adverse events between groups receiving an active intervention or placebo or no prophylaxis (see online supplemental file 10). Moreover, there seems to be no consistent difference in adverse events between groups receiving any active interventions.

Table 1 Network meta-analysis results comparing the effects of different interventions for clinically important upper GI bleeding (N=94 RCTs) including risk ratios (RR) and 95% CIs

Antacids														
1.13 (0.49,2.58)	**Anticholinergic**													
0.90 (0.38,2.13)	0.80 (0.25,2.56)	**Bioflavonoids**												
0.86 (0.60,1.23)	0.76 (0.34,1.70)	0.95 (0.39,2.32)	**Cimetidine**											
2.52 (0.75,8.47)	2.24 (0.55,9.16)	2.79 (0.65,12.00)	2.94 (0.91,9.51)	**Esomeprazole**										
0.91 (0.37,2.26)	0.81 (0.26,2.56)	1.01 (0.30,3.38)	1.06 (0.44,2.58)	0.36 (0.10,1.27)	**Famotidine**									
3.59 (0.76,16.89)	3.19 (0.57,17.73)	3.97 (0.70,22.44)	4.19 (0.89,19.76)	1.42 (0.21,9.83)	3.94 (0.69,22.61)	**Ranitidine +Antacids**								
4.67 (0.50,44.02)	4.14 (0.39,43.53)	5.16 (0.48,56.02)	5.44 (0.58,50.97)	1.85 (0.16,21.81)	5.12 (0.55,47.86)	1.30 (0.09,19.31)	**Lansoprazole**							
1.44 (0.82,2.53)	1.28 (0.52,3.13)	1.59 (0.60,4.25)	1.68 (0.97,2.89)	0.57 (0.16,2.04)	1.58 (0.60,4.18)	0.40 (0.08,1.98)	0.31 (0.03,3.00)	**Omeprazole**						
0.65 (0.30,1.43)	0.58 (0.20,1.66)	0.72 (0.23,2.23)	0.76 (0.35,1.64)	0.26 (0.07,1.01)	0.72 (0.26,1.97)	***0.18 (0.03,0.99)***	0.14 (0.01,1.41)	0.45 (0.19,1.08)	**Pantoprazole**					
0.38 (0.16,0.89)	0.34 (0.11,1.06)	0.42 (0.13,1.38)	0.44 (0.19,1.04)	***0.15 (0.04,0.64)***	0.42 (0.12,1.39)	***0.11 (0.02,0.61)***	***0.08 (0.01,0.88)***	***0.26 (0.10,0.70)***	0.58 (0.19,1.77)	**Prostaglandin analogues**				
8.03 (0.39,166.07)	7.12 (0.32,159.09)	8.88 (0.39,203.69)	9.35 (0.45,193.45)	3.18 (0.12,81.33)	8.80 (0.38,202.06)	2.23 (0.08,65.45)	1.72 (0.04,72.87)	5.57 (0.27,116.15)	12.28 (0.55,272.60)	21.15 (0.92,485.87)	**Rabeprazole**			
0.89 (0.60,1.34)	0.79 (0.36,1.75)	0.99 (0.40,2.41)	1.04 (0.70,1.55)	0.35 (0.10,1.20)	0.98 (0.40,2.40)	0.25 (0.05,1.17)	0.19 (0.02,1.80)	***0.62 (0.39,0.98)***	1.36 (0.63,2.95)	2.35 (0.96,5.77)	0.11 (0.01,2.24)	**Ranitidine**		
0.89 (0.63,1.25)	0.79 (0.35,1.77)	0.98 (0.42,2.28)	1.03 (0.72,1.47)	0.35 (0.11,1.17)	0.97 (0.40,2.34)	0.25 (0.05,1.12)	0.19 (0.02,1.78)	0.61 (0.36,1.04)	1.35 (0.63,2.92)	2.33 (0.97,5.62)	0.11 (0.01,2.26)	0.99 (0.71,1.39)	**Sucralfate**	
0.89 (0.19,4.13)	0.79 (0.15,4.24)	0.99 (0.18,5.55)	1.04 (0.22,4.81)	0.35 (0.05,2.40)	0.98 (0.17,5.51)	0.25 (0.03,2.11)	0.19 (0.01,2.80)	0.62 (0.13,2.91)	1.36 (0.26,7.23)	2.35 (0.42,13.26)	0.11 (0.01,2.24)	1.00 (0.23,4.39)	1.01 (0.22,4.59)	**Teprenone**
0.48 (0.33,0.68)	***0.42 (0.19,0.93)***	0.53 (0.22,1.28)	***0.56 (0.40,0.77)***	***0.19 (0.06,0.63)***	0.52 (0.22,1.24)	***0.13 (0.03,0.62)***	***0.10 (0.01,0.94)***	***0.33 (0.20,0.56)***	0.73 (0.36,1.47)	1.26 (0.53,2.99)	0.06 (0.00,1.22)	***0.54 (0.38,0.76)***	***0.54 (0.39,0.75)***	0.54 (0.12,2.45)	**Placebo**

RR<1 means the bottom-right intervention is protective.

*Bold font indicates statistically significant effect estimates

GI, gastrointestinal; RCTs, randomised controlled trials.

Table 2 Summary of findings of the network meta-analysis for primary outcome (clinically important upper gastrointestinal bleeding)

Outcome	CoE	Classification	Intervention	RR (95% CI)	Anticipated absolute effect (95% CI)	SUCRA	Number of studies (participants)
Clinically important upper gastrointestinal bleeding	High (moderate to high)	The most effective	Ranitidine+antacids	0.13 (0.03 to 0.62)*	Not Applicable†	85.3	Not applicable†
			Cimetidine	0.56 (0.40 to 0.77)*	79 fewer per 1000 (from 108 fewer to 41 fewer)	37.9	13 (1288)
			Ranitidine	0.54 (0.38 to 0.76)*	88 fewer per 1000 (from 118 fewer to 46 fewer)	40.8	12 (871)
			Antacids	0.48 (0.33 to 0.68)*	87 fewer per 1000 (from 113 fewer to 54 fewer)	50.7	8 (708)
			Sucralfate	0.54 (0.39 to 0.75)*	58 fewer per 1000 (from 78 fewer to 32 fewer)	40.4	8 (698)
		Inferior to the most effective/superior than the least effective	–	–		–	
		Among the least effective	Prostaglandin analogues	1.26 (0.53 to 2.99)‡	27 more per 1000 (from 49 fewer to 206 more)	6.5	1 (58)
	Low (low to very low)	May be the most effective	Omeprazole	0.33 (0.20 to 0.56)*§¶	25 fewer per 1000 (from 30 fewer to 16 fewer)	69.9	3 (371)
		May be inferior to the most effective/superior than the least effective	Lansoprazole	0.10 (0.01 to 0.94)*§	90 fewer per 1000 (from 99 fewer to 6 fewer)	84.2	1 (120)
			Esomeprazole	0.19 (0.06 to 0.63)	Not Applicable†	80.8	Not Applicable†
			Pirenzepine	0.42 (0.19 to 0.93)*§	56 fewer per 1000 (from 79 fewer to 7 fewer)	54.8	2 (131)
		May be among the least effective	Bioflavonoids	0.53 (0.22 to 1.28)‡	Not applicable†	43	Not applicable†
			Pantoprazole	0.73 (0.36 to 1.47)*‡	10 fewer per 1000 (from 24 fewer to 18 more)	24.8	4 (3784)
			Famotidine	0.52 (0.22 to 1.24)*§**	53 fewer per 1000 (from 86 fewer to 26 more)	42.5	2 (196)
			Rabeprazole	0.06 (0.00 to 1.22)††	Not applicable†	87.4	Not applicable†
			Teprenone	0.54 (0.12,2.45)	Not applicable†	42.1	Not applicable†

*Downgraded one level for risk of bias because the trial(s) included in the analysis was/were at high risk of bias.

†Represents evidence coming only from indirect comparisons.

‡Downgraded one level for imprecision because the credible intervals were wide (included clinical benefit and harms).

§Downgraded one level for imprecision because the sample size was small.

¶Downgraded two levels for incoherence.

**Downgraded one level for inconsistency because there was evidence of statistical heterogeneity.

††Downgraded two levels for imprecision because the credible intervals were very wide (included clinical benefit and harms).

RR, relative risk; SUCRA, surface under the cumulative ranking curve.

Subgroup and sensitivity analyses are reported in online supplemental file 11,12.

Discussion

In this systematic review and NMA of pharmacological interventions for preventing upper GI bleeding in ICU patients, we included 123 studies. We found that for the prevention of clinically important upper GI bleeding, cimetidine, ranitidine, antacids, sucralfate or a combination of ranitidine and antacids seem to be the most effective intervention. However, there is no compelling evidence that suggests that any interventions clearly impacts on the risk of ventilator-associated pneumonia, nosocomial pneumonia or other relevant outcomes, which might further warrant their usage in ICU patients. This finding is also reflected in subgroups of participants with bleeding disorders, participants who had pneumonia at the time of admission or infants and children. Only for the number of participants requiring blood transfusions, there seems to be a beneficial effect of antacids compared with placebo. The various interventions that are compared in this review are available worldwide and can plausibly prevent bleeding from stress ulcers in ICU patients.

Evidence gaps indicate that further research would be helpful in guiding decision-making. One of these gaps reflects lack of evidence about the effects of bleeding prophylaxis on different population subgroups, including people with pneumonia at the time of ICU admission, as well as the effects of cointerventions such as different feeding regimens, antibiotics, etc, on the effectiveness of bleeding prophylaxis. Furthermore, more evidence from RCTs is needed on the effects of PPIs on *C. difficile* infection-related diarrhoea. This adverse event has been observed in non-randomised studies but rarely in RCTs. *C. difficile* infection-related diarrhoea was not included as an outcome of this review at the stage of formulating the review protocol. We identified only eight studies that reported on this adverse event.[4 5 12 32 61 142 143 163]

In recent years, several systematic reviews have investigated the risk–benefit profile of bleeding prophylaxis in ICU patients.[6 8–10 19] Their conclusions about the beneficial effect of stress ulcer prophylaxis on clinically important upper GI bleeding in ICU patients varied. The scope of these reviews mostly focuses on a limited number of interventions compared with each other or of one or with placebo or no prophylaxis and our review complements a comprehensive and up-to-date evidence base for this important medical topic. Alquarini *et al*[16] compared sucralfate versus H2RAs in ICU patients for prevention of upper GI bleeding and the incidence of pneumonia and found no difference between the two treatments in the occurrence of upper GI bleeding but found a lower incidence of nosocomial pneumonia in the sucralfate arm, which confirms the findings of this review[6] that compared the effects of H2RAs, PPIs to placebo in ICU patients. The systematic review and trial sequential analysis included 42 trials with 6899 participants. In the trial sequential analysis, no clear effect of prophylactic treatment on the occurrence of upper GI bleeding was identified.[180] Krag *et al*[181] conducted a systematic review using Cochrane methods and compared the effects of H2RAs or PPIs versus placebo or no treatment. They reported lower risk of upper GI bleeding in the pooled effect of all studies with treatment versus placebo or no treatment. However, they emphasised that this result was not maintained in an analysis of low risk of bias studies only. Similar to our findings, risk of pneumonia was not significantly different between treatment and no prophylaxis or placebo. Recently conducted RCT[4 22] seemed to be adequately powered to detect meaningful differences in the effect on clinically important upper GI bleeding.

We included studies that investigated the effects of bleeding prophylaxis in a broad spectrum of participants with different reasons for admission and in a variety of countries and ICU settings. The interventions in the studies varied as well as the outcome definitions and their measurement. Bleeding definition as reported in the included trials was based on evidence of upper GI bleeding such as notable haemodynamic shifts without alternative explanations, requirement of transfusion exceeding two units of blood, substantial decline in haemoglobin levels, detection of bleeding during upper GI endoscopy or necessity for surgical intervention to manage bleeding. Several aspects of study planning and execution might have been subject to the long duration in which the included studies were conducted and changing medical standards for administering interventions and assessing outcomes. Hence, our findings must be interpreted with caution not only because 80 out of 123 included studies were published before the year 2000. Likewise, the baseline risk for our outcomes of interest might have changed. Such (temporal) changes could have contributed to heterogeneity and increased the uncertainty of findings. However, exploratory sensitivity analyses by year of publication not reported in further detail did not alter the consistency of study results nor the direction of effect.

Results from subgroup analyses must be interpreted with caution because the number of included studies is relatively small and the power to detect any statistical differences in effect is limited. Information from such subgroup and sensitivity analyses would be relevant for guiding decision-making in practice. Lastly, our NMA method was established post hoc and was based on established methodology in the literature.

The overall certainty of the evidence ranged from moderate to very low for most outcomes. The main reasons for downgrading the certainty of evidence were the risk of bias in the included studies and imprecision of the direct and network estimate.

Conclusions

This review found evidence of moderate certainty to show that a number of interventions might be effective in preventing upper GI bleeding in ICU patients compared with placebo or no prophylaxis. Also, the effect of any intervention on the prevention of nosocomial pneumonia, all-cause mortality in the ICU, all-cause mortality in the hospital, duration of the stay in the ICU, duration of intubation and serious adverse events remains unclear with no intervention seeming more effective as compared with placebo, no prophylaxis or any other intervention.

Our research emphasises that decisions in practice should be based on individual assessments of patient needs and underlying conditions. Overall, the local context and resources must be considered in selection of treatment.

Our findings are mostly based on evidence of low and very low certainty except for the primary outcomes. Given that antacids are almost no longer used in practice, only good quality research to assess the risk of nosocomial pneumonia, serious adverse events, *C. difficile* infections and other harms in patients receiving sucralfate, H2RAs or PPIs might be useful to ascertain the effectiveness of these interventions.

Provided H2RAs and PPIs are the drugs used most often, the effect of PPIs on any adverse event including nosocomial pneumonia and mortality should be investigated in meta-analyses that clearly take into consideration the underlying conditions of study participants and any concomitant intervention.

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