Journal of Critical Care 71 (2022) 154093

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Prophylactic acid suppressants in patients with primary neurologic injury: A systematic review and meta-analysis of randomized controlled trials

Marietou Daou, MSc [a], Joanna C. Dionne, MD PhD [b,c], Jennifer F.T. Teng, PharmD [d,e], Shaurya Taran, MD [f,g], Nicole Zytaruk, RN [h], Deborah Cook, MD MSc [b,c,h], M. Elizabeth Wilcox, MD PhD [a,f,g,*]

[a] Toronto Western Hospital, Toronto, Ontario, Canada
[b] Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[c] Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[d] Department of Pharmacy, University Health Network, Toronto, Canada
[e] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada
[f] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
[g] Department of Medicine (Respirology), University Health Network, Toronto, Canada
[h] St. Joseph's HealthCare Hamilton, Hamilton, Ontario, Canada

ARTICLE INFO

Keywords:
Stress ulcer prophylaxis
Neurocritical care
Upper gastrointestinal bleeding

ABSTRACT

Purpose: Neurocritical care patients are at risk of stress-induced gastrointestinal ulceration. We performed a systematic review and meta-analysis of stress ulcer prophylaxis (SUP) in critically ill adults admitted with a primary neurologic injury.

Materials and methods: We included randomized controlled trials (RCTs) comparing SUP with histamine-2-receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) to placebo/no prophylaxis, as well as to each other. The primary outcome was in-ICU gastrointestinal bleeding (GIB). Predefined secondary outcomes were all-cause 30-day mortality, ICU length of stay (LOS), nosocomial pneumonia, and other complications.

Results: We identified 14 relevant trials enrolling 1036 neurocritical care patients; 11 trials enrolling 930 patients were included in the meta-analysis. H2RAs resulted in a lower incidence of GIB as compared to placebo or no prophylaxis (Risk ratio [RR] 0.42, 95% CI 0.30–0.58; $p < 0.001$); PPIs with a lower risk of GIB compared to placebo/no prophylaxis (RR 0.37, 95% CI 0.23–0.59; $p < 0.001$). No significant difference was observed in GIB comparing PPIs with H2RAs (RR 0.53, 95% CI 0.26–1.06; $p = 0.07$; $I^2 = 0\%$).

Conclusions: In neurocritical care patients, the overall high or unclear risk of bias of individual trials, the low event rates, and modest sample sizes preclude strong clinical inferences about the utility of SUP.

1. Introduction

Stress ulcer prophylaxis (SUP) is provided as standard practice to prevent gastrointestinal bleeding (GIB) in critically ill patients at high risk of developing stress ulceration [1-3]. However, evidence regarding the benefits and harms of SUP in the general ICU population is variable, possibly related to evolving standards in care such as earlier administration of enteral nutrition [4], modern ventilation strategies and the risk of bias in prior trials. Recent studies show that SUP may not prevent clinically important GIB or decrease mortality [5,6], and may in fact may increase the risk of adverse events, such as ventilator-associated pneumonia (VAP) [7] and *Clostridioides difficile* infections [8]. There are few recent, high quality randomized clinical trials (RCTs) assessing the efficacy and safety of SUP in critically ill patients conducted in accordance with current clinical practices; the most recent trials seem to indicate less efficacy of SUP in the ICU, specifically in reducing GIB or in ICU mortality, albeit with important heterogeneity [9-11]. Currently, a large randomized controlled trial (RCT) is ongoing, *Re*-Evaluating the Inhibition of Stress Erosions (REVISE) Trial, to determine the adequacy, efficacy and safety of pantoprazole administration compared to placebo in mechanically ventilated adult patients (https://clinicaltrials.gov/ct2/show/NCT03374800).

* Corresponding author at: Department of Medicine; Division of Respirology, Toronto Western Hospital, McLaughlin Wing 2-411M, 399 Bathurst Street, Toronto, ON M5T 2S8, Canada.
E-mail address: elizabeth.wilcox@mail.utoronto.ca (M.E. Wilcox).

https://doi.org/10.1016/j.jcrc.2022.154093
0883-9441/

A unique subpopulation within the general ICU are patients with primary neurologic injury (e.g., ischemic stroke or spinal cord injury). Following primary neurologic injury, patients may be more susceptible to GIB due to delays in enteral feeding, higher aspiration risk, and receipt of anti-platelet agents, anti-coagulants, or both [12,13]. Further, neurologic patients may have a higher risk of morbidity and mortality from GI bleeding due to low Glasgow Coma Scale (GCS) [14,15], injury severity, organ failure [16], and coagulopathy [6,17]. Additional pathophysiologic mechanisms contributing to heightened bleeding risk include elevated intracranial pressure (ICP), vagally-mediated acid secretion, and hypoperfusion of the gastric mucosa, can lead to disruption of the gastric mucosal barrier and elevated gastric secretions [18,19]. Therefore, it is possible that the risk: benefit ratio of SUP for patients with primary neurologic injury, as compared to general ICU patients, may differ.

We conducted a systematic review and meta-analysis of RCTs to assess the influence of SUP with proton pump inhibitors (PPI) or H2 receptor antagonists (H2RAs), compared to each other or no prophylaxis or placebo, on risk of GI bleeding in patients >18 years of age admitted to the ICU with a primary neurologic injury.

2. Methods

We followed the recommendations from the Cochrane Collaboration [20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see eTable 1) [21].

2.1. Eligibility criteria

We included RCTs comparing stress ulcer prophylaxis with a PPI or H2RA (in any dose, formulation, timing, and duration) vs. placebo or no prophylaxis in critically ill adults (as defined by the included trials), as well as RCTs comparing PPIs vs. H2RAs, admitted to the ICU for a primary neurological condition such as traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), ischemic stroke, anoxic brain injury, spinal cord injury, central nervous system (CNS) tumour or other acute neurological injury or surgery. For studies conducted in mixed adult ICUs, we required at least 50% of patients to have a primary neurological injury to be considered further. Quasi-randomized and cross-over trials were excluded. No restrictions were applied to publication language, publication status, sample size, or reported outcome.

2.2. Literature search

In consultation with a medical librarian, we searched the Cochrane Library, MEDLINE and EMBASE. We also hand-searched relevant trial reports and other systematic reviews and meta-analyses for relevant trials. The full systematic search strategies are available in eTable 2. The literature search was updated on 1st November 2021. The development of our search strategy was iterative; initial review of manuscripts yielded with the use of specific terms such as TBI, anoxic brain injury, and spinal cord injury increased the sensitivity of the search without impacting the number of trials of interest (i.e., those relating to the intervention of interest) and hence the terms were removed from the final search strategy.

2.3. Study selection and data extraction

Working in pairs, four review authors (MD or JT or JCD or MEW) independently and in duplicate screened articles by title and abstract. Relevant studies were assessed in full text. Discrepancies were resolved through consensus.

The same 4 authors independently extracted information from the included RCTs using a pretested data collection form. Extracted data included trial characteristics (year of publication and country), participant characteristics (type of patients, type of ICUs, age, mechanical ventilation (yes/no), type of intervention (name, dosing, duration, and route of administration), comparators and outcome.

2.4. Outcomes

Our primary outcome was GI bleeding (defined as hematemesis, coffee ground nasogastric aspirate, or melena) developing at any point during ICU admission. In secondary analyses, we also separately examined overt GIB, clinically significant GIB, and occult bleeding, as outcome definitions used in prior reports. Predefined secondary outcomes were all-cause 30-day mortality, ICU length of stay (LOS), nosocomial pneumonia, and other complications (as reported in the primary studies); for all secondary outcomes the accepted definitions used were those reported in the included studies. For each analysis, based on availability of comparable data, H2RAs and PPIs were compared to placebo or no prophylaxis and to each other. Data estimates were reported as presented in the original study with no data conversion.

2.5. Meta-analyses

We calculated pooled risk ratios (RR) and 95% confidence intervals (CIs) for dichotomous outcomes and pooled weighted mean differences (WMD) and 95% CIs for continuous outcomes. All meta-analyses were performed using random-effects models [22]. Continuous variables are expressed as mean (standard deviation, SD), unless otherwise indicated. We assessed heterogeneity among trials using I^2, the percentage of total variability across studies attributable to heterogeneity rather than chance [23,24]. Heterogeneity was reported as low (I^2 = 25%–49%), moderate (I^2 = 50%–74%), or high (I^2 = 75%), in accordance with published guidelines [23]. For the primary outcome of GIB, we inspected a funnel plot for the presence of publication bias. All meta-analyses were performed using Review Manager 5.1.4 (The Cochrane Collaboration, Oxford, England).

2.6. Risk of bias

The Revised Cochrane risk-of-bias tool for RCTs (RoB 2) was used to evaluate the methodological quality of each study [25]. Two authors (MD, JCD or MEW) independently and in duplicate assessed the risk of systematic errors (bias) in the included trials, with discrepancies resolved by consensus. We assessed the risk of bias across 5 domains: (D1) arising from the randomization process; (D2) due to deviation from intended interventions (effect of adhering to intervention); (D3) in missing outcome data; (D4) in measurement of the outcome; and (D5) in selection of the reported result. If one or more domains were adjudicated as "high risk" in at least one domain or "some concerns" for multiple domains, we classified the trial as having an overall high risk of bias [25].

3. Results

3.1. Study flow

The search strategy yielded 3333 citations (see Fig. 1). Of 180 articles retrieved for full-text evaluation, 166 were excluded; 14 trials enrolling 1036 patients met criteria for inclusion [14,26-38] and 11 trials enrolling 930 patients were included in the meta-analysis [14,26-30,32,34-37]. The primary reasons to exclude articles related to the study design, population, and outcomes outside the scope of interest. The study by Zhang et al. 2014 [39], that may have met inclusion criteria, as it was included in a previous systematic review [17], was excluded from our analysis as a high-level translation could not be obtained to ascertain the definition of GIB used by the investigators or could the quality of the trial be assessed.

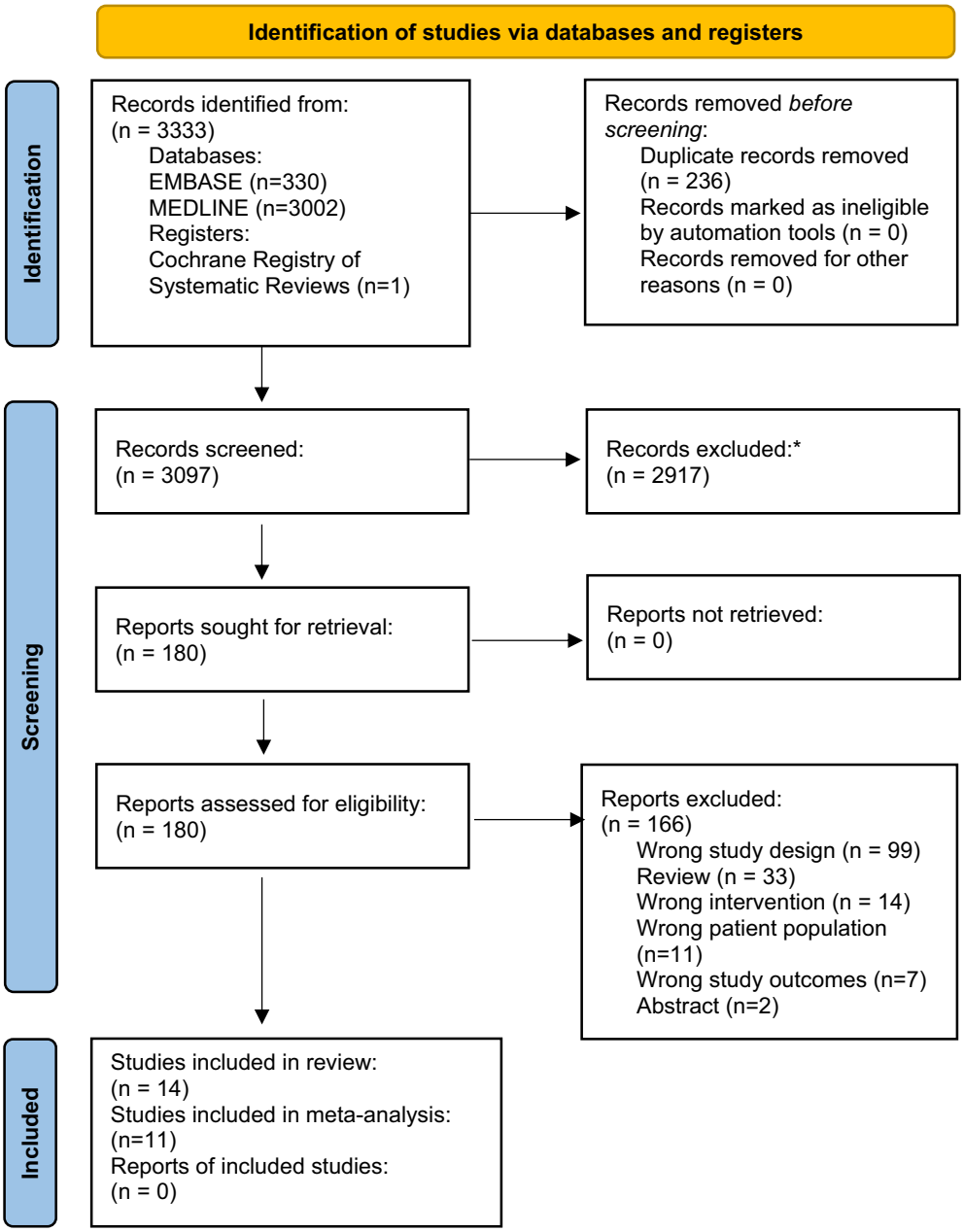


Fig. 1. Study flow diagram.
*No automation tools were used to exclude records; selection process was conducted by reviewers.

3.2. Description of included studies

Included trials were published between 1980 and 2019. Of the included trials, 5 (36%) were performed in the United States, 2 were performed in China (14%), 2 were performed in India (14%), and 1 each in Czech Republic, Taiwan, Switzerland, Iran, and Indonesia. A total of 5 trials examined H2RAs compared to placebo [14,27,28,30,36], 2 trials examined H2RAs compared to no intervention [32,37], 1 trial examined PPIs compared to no intervention [29], and 4 trials compared PPIs to H2RAs [26,34,35,38] (See Table 1). Of note, 1 trial examined PPIs and H2RAs as a 3-arm trial with a placebo group [35] and 2 trials compared medications in the same pharmacological class (PPIs) [31,33]. Additionally, 2 trials [33,36] evaluated sucralfate as an intervention, but we did not include this group in the analysis. Three trials were not included in the meta-analysis as they lacked comparable data: 2 trials compared medications in the same pharmacological class [31,33] and 1 trial did not report on clinically important outcomes [38]. The median duration of intervention across all trials was 6 days [14,26-28,30-38]. In 6 trials, early enteral feeding practices in the participating ICUs was reported as "standard of care" [26,29,34,36-38]; in 4 trials, patients fasted during the study period [31] or no enteral feeding was allowed [14,27,35]; and, in the remaining trials, no details were provided with regards to enteral nutrition [28,30,32,33].

Of the 930 patients included in the analysis, 486 patients (52%; $n = 6$ trials) had TBI [14,26,27,30,32,37], 337 patients (36.2%; $n = 5$ trials) were admitted with ICH [26,34-37], 70 patients (7.5%; $n = 2$ trials) had cerebrovascular disease (e.g., ischemic stroke) [28,34], 43 (4.5%; n = 2 studies) reported on patients with either a primary CNS malignancy, CNS infection or hydrocephalus [28,34] and 7 patients (0.75%; n = 2 trials) were admitted with spinal cord injury [26,31]. The median

Table 1
Characteristics of included trials.

Study Country Setting Recruitment period	Sample size (N) Age, mean (SD) Sex (male), No. (%)	Inclusion criteria Exclusion criteria	Patient population, No. (%) Injury Severity Score, mean (SD) GCS mean (SD) ICU length of stay, days, mean (SD) Duration of MV, days, mean (SD)	LTFU[a] No. (%) ICU mortality No. (%) 30-day survival No. (%)	Intervention Comparator	Maximum treatment period Maximum observation period for GI bleeding Adverse events	Enteral nutrition, No. (%) Details	Primary endpoint Secondary endpoints	GI bleeding definition
Brophy et al. 2010 [26] United States Single centre; Academic trauma centre August 1999 –April 2005	51 40 (19.91) 37 (73)	Neurosurgical ICU admission with SUP prescription during the study period; baseline gastric pH < 4, at least one risk factor for GI bleeding (MV, head injury with altered mental status, acid-base disorder, multiple systems trauma, coagulopathy, multiple surgical procedures, hypotension >1 h, sepsis) Active GI injury, history of gastric ulcer, age < 18 years, use of antisecretory agents during current admission prior to enrolment, allergy to study drug, pregnancy, renal compromise, anticipated SUP for <3 days	ICH 10 (19.6) TBI 28 (54.9) SAH 8 (15.7) SDH 1 (2) SCI 4 (7.8) - Median GCS: 5.5: 39/51 (76%) had GCS < 9 - -	0 (0) 1 (2) - -	Famotidine 20 mg every 12 h IV Lansoprazole 30 mg every 24 h NG tube	72 h 24 h after discontinuation of SUP, ICU discharge or death 5 (10%) of patients experienced thrombocytopenia	41 (80) Enteral feeding started on day 1 for 20/51 patients (39%); day 2: 37/51 (73%) of patients received enteral nutrition; day 3: 40/51 (78%)	Time gastric pH ≥ 4 and gastric residuals <28 mls UGIB Thrombocytopenia	Clinically significant bleeding defined as presence of 1 of: endoscopic evidence of stress-related mucosal bleeding, bright red blood aspirates from NG tube that did not clear after lavage, or overt bleeding (hematemesis, bloody gastric aspirate, melena or hematochezia) plus decrease in blood pressure of 20 mmHg, or a decrease of 2 g/dL in hemoglobin and 2 units of blood transfused within 24 h
Burgess et al. 1995[27] United States Single centre; Academic SICU February 1988 – November 1988	34 36.45 (standard error 4.1) 25 (74)	Severe head injury and GCS ≤10 Active PUD, other GI injury, current antiulcer therapy, any oral intake	TBI 34 (100) 31 (range 25–41) 7.35 (range 3–10) - -	0 (0) 1 (3) -	Ranitidine 6.25 mg/h IV continuos infusion Placebo	72 h 48 h after discontinuation of SUP No adverse events related to ranitidine reported	0 (0) No enteral feeding allowed	UGIB ICU mortality Intragastric pH Ranitidine-associated adverse events	UGIB defined as hematemesis, hematochezia, bright red blood aspirates from NG tube or coffee-ground aspirates from NG tube plus a 5% decrease from baseline in hematocrit at least 8 h after initiation of study drug
Chan et al. 1995 [28] China Single centre; Academic SICU July 1988–December 1989	101 61 (1.3) 54 (53)	Non-traumatic neurosurgical admission with 2 or more risk factors for GI bleeding (preoperative coma, inappropriate secretion of ADH, major postoperative complications requiring reoperation, age > 60 years, and/or CNS infection) Presence of GI bleeding before surgery, history of chronic GI	CVD 69 (68.3) Brain tumour 29 (28.7) CNS infection 3 (3) Hydrocephalus 10 (9.9) -	0 (0) - - 	Ranitidine 50 mg every 6 h IV + 150 mg orally every 12 h when patients ready for enteric feeding Placebo *concomitant medication:	- - No adverse events reported; tolerated endoscopy without incident	- Details not specified	UGIB All-cause mortality Ranitidine-associated adverse events Nosocomial pneumonia Modified Glasgow	Endoscopically documented acute lesion with or without bleeding requiring blood transfusion and/or surgery for acute perforated ulcers or treatment of peritonitis within 12 h of surgical intervention

		disease and ulcers, major heart, lung, kidney, blood or liver disease	6 (range 3–8) - 4.6 (0.6)		dexamethasone 4 mg q6 hrs			Outcome Scale at 6 months (independent assessment as to whether disability secondary to GI tract lesion)	
Fang et al. 2014 [29] China Single centre; — May 2011–May 2013	120 47.09 (5.44) 81 (67.5)	Severe TBI; unable to follow commands Known peptic ulcers, coagulopathy, or other severe systemic disease	TBI 120 (100) - - - -	0 (0) - - -	Omeprazole 40 mg every 12 h IV or Lansoprazole 30 mg every 12 h IV plus sucralfate 1.0 g tablet every 6 h No intervention *concomitant medications: each patient received steroids (dexamethasone or methylprednisolone)	- - -	120 (100) Patients in group A and C were given early enteral support within 12–24 h after admission. Patients in group B were given late enteral support within 48–72 h after admission	UGIB Gastric pH Ulcer healing time Blood sugar	Hematemesis, blood in the stool, or fresh blood aspirates, coffee-ground aspirates or positive stool occult blood test
Halloran et al. 1980 [30] United States Single centre; — July 1977–March 1979	50 30.1 (range 8–62) 41 (82)	Admission within 12 h of severe head injury, unable to obey simple commands after closed head injury Apnea plus fixed dilated pupils and no motor response to painful stimuli at baseline, PUD, pregnancy, advanced liver or renal disease	TBI 50 (100) - - - -	0 (0) - - 	Cimetidine 300 mg every 4 h IV or orally once enteral feeding or a diet was started Placebo	21 days - -	- Details not specified	UGIB Gastric pH	Bright red blood or a 4 plus positive guaiac in the gastric aspirate for three consecutive 8 h periods (exclusive of first day after injury) if no oropharyngeal source of bleeding present
Jones et al. 1994 [31] United States Single centre; Academic surgical-trauma ICU December 1990–May 1991	20 28 (range 21–41) 13 (65)	Trauma or surgical ICU admission, age > 18 years, within 72 h of traumatic injury, 2 consecutive hourly gastric pH measurements <4 prior to treatment History of gastric malignancy, sepsis or burn injury, treatment with antacids or sucralfate in the previous 4 h, treatment with H2RA in the previous 8 h, allergy to study drug, history of oesophageal varices, previous ulcer surgery with the exception of a simple oversew, Zollinger-Ellison syndrome or other pathologic hypersecretory conditions, pregnancy, serum creatinine concentration > 176.8 mmol/L	TBI 11 (55) SCI 3 (15) Multiple trauma 6 (30) 25 (range 18–33) - - -	0 (0) - - 	Famotidine 20 mg over 15 min every 12 h IV bolus administration, increased to a maximum of 80 mg/24 h to maintain gastric pH < 4 Famotidine 1.7 mg/h IV continuous infusion, increased to a maximum of 80 mg/24 h to maintain gastric pH < 4	1 day - No adverse events reported with famotidine	0 (0) Patients fasted during the study period	UGIB Gastric pH Famotidine-associated adverse effects	Frank bleeding defined as hematemesis, bloody gastric aspirate, melena or hematochezia Clinically important bleeding defined as presence of frank bleeding and hypotension or a 20 g/L drop in hemoglobin requiring transfusion
Kaushal et al. 2000 [32] India Single centre; Neurosurgical ICU	50 34.63 (13.46) 45 (90)	Admission for closed head injury <24 h duration, GCS ≤ 10, need for intubation History of acid peptic disease, UGIB, use of ulcer-modifying drugs in the 4 preceding weeks, significant renal/hepatic disease, or bleeding	TBI 50 (100) - - -	0 (0) 18 (36) - 	Famotidine 20 mg every 12 h IV No intervention	- 15 days -	- No details mentioned	UGIB Acute hospital mortality	Hemorrhage was graded as grade 0 if test for occult blood was negative; grade 1 if test for occult blood was positive; grade 2 if there was also red or brown discolouration of the aspirate; and grade 3 if severity of hemorrhage necessitated blood transfusion

(continued on next page)

Table 1 (*continued*)

Study Country Setting Recruitment period	Sample size (N) Age, mean (SD) Sex (male), No. (%)	Inclusion criteria Exclusion criteria	Patient population, No. (%) Injury Severity Score, mean (SD) GCS mean (SD) ICU length of stay, days, mean (SD) Duration of MV, days, mean (SD)	LTFU[a] No. (%) ICU mortality No. (%) 30-day survival No. (%)	Intervention Comparator	Maximum treatment period Maximum observation period for GI bleeding Adverse events	Enteral nutrition, No. (%) Details	Primary endpoint Secondary endpoints	GI bleeding definition
		diathesis							
- Krakamp et al. 1989 [33] - Germany - Single centre; — - Lee et al. 2014 [34] 57.7 (16.8) Taiwan Single centre; Academic neurosurgical ICU March 2007–March 2010	- 30 - - 60 36 (60)	- Neurosurgical admission, age ≥ 20 years, expected survival after first two days in ICU UGIB, sepsis and pneumonia Neurosurgical admission Age ≤ 18 years, allergy to study drug, impossibility to be fed via NG tube, GI bleeding at baseline	- TBI 30 (100) - - - - ICH 58 (96.7) Cerebral infarct 1 (1.7) Brain tumour 1 (1.7) - 7.65 (4.3) 23.45 (12.25)	- 0 (0) - - 0 (0) - 56 (93.4)	- Combination of 200 mg of ranitidine and placebo 200 mg IV every 6 h Combination of 200 mg of ranitidine and 20 mg pirenzepine IV every 6 h Esomeprazole 40 mg every 24 h NG tube Famotidine 20 mg every 12 h IV	- 7 days - - - 7 days -	- - No details mentioned - 60 (100) Most patients started enteral feeding after ICU admission if not contraindicated	- UGIB Gastric pH Sepsis Nosocomial pneumonia UGIB (overt and occult) 30-day mortality ICU length of stay Nosocomial pneumonia	- Hematemesis, melena, gastric aspirates in NG tube, hemoglobin drop of at least 2% in 48 h UGIB defined as tarry stool, hematemesis, >60 ml of coffee-ground aspirates from NG tube, or decreased hemoglobin level > 2 g/dL with proved lesions by endoscopic examination Occult bleeding defined as positive stool occult blood test
- Liu et al. 2013 [35] - China 100 (60) Single centre; Academic neurosurgical ICU April 2006–December 2008	- 165 - - - -	- Age > 18 years, neurosurgical admission within 72 h of CT-proven ICH, NG tube in place, baseline gastric pH <4 on 2 consecutive determinations, negative gastric occult blood testing at baseline Arteriovenous malformation or aneurysmal hemorrhage, history of PUD, high-risk of swallowing blood, antiplatelet or anticoagulation therapy, renal insufficiency, thrombocytopenia <30,000/ml, death within 72 h after ICH	- ICH 165 (100) - - - - -	- 19/184 (10.3) - - - -	- Omeprazole 40 mg every 12 h IV Cimetidine 300 mg every 6 h IV Placebo	- 7 days Bleeding within 15 days of ictus No adverse events related to omeprazole	- 0 (0) No enteral feeding allowed	- UGIB 30-day mortality Gastric pH Nosocomial pneumonia Sepsis Omeprazole-related adverse events	- Hematemesis, coffee-ground aspirates per NG tube or melena, proven by positive results of gastric occult blood testing or faecal occult blood testing with or without hemodynamic instability resulting from gross bleeding that needed transfusion
Metz et al. 1993 [14]	167	Severe TBI (GCS ≤10), age ≥ 18 years, NG tube in place, expected	TBI 167 (100)	0 (0)	Ranitidine 6.25 mg/h IV	5 days	0 (0)	UGIB	Gastroccult positive NG tube aspirates and coffee-ground

	33.95	ICU stay ≥72 h, within 24 h of injury		-	continuos infusion	15 days	No enteral nutrition allowed	30-day mortality	aspirates present for the last 8 h, minimum of 50 ml bright red blood
United States	(1.88)		-						per NG tube, hematemesis in the last 8 h, hemoccult positive stool, melena, or hematochezia with or without endoscopic or surgical confirmation of an UGIB source
		Active GI bleeding at baseline,		-	Placebo	-		Nosocomial	
Multi centre; 10	123	severe burns (>20% of body surface	6 (range 3–10)					pneumonia	
sites	(74)	area), renal insufficiency, PUD in the							
		last 6 months, thrombocytopenia	-						
January		<50,000/ml, SUP within 24 h of							
1990–September		study entry	-						
1991									
Misra et al. 2005	92	ICH; within 7 days of ictus	ICH	35/176	Ranitidine	-	-	UGIB	Gross blood, coffee-ground aspirates
[36]			92(100)	(20)[c]	50 mg every 8 h IV				from NG tube, hematemesis or
	57.2 (−) [b]	Arteriovenous malformation,				-	Patients received about	30-day mortality	melena with or without blood transfusion
India		aneurysmal bleed, bleeding and	-	-	Placebo		2000 cal, 2–2.5 L fluids		
	63	coagulation disorders, hepatic and				-		Sepsis	
Single centre; −	(68)	renal failure, history of PUD,	9.8 (range	74(80)					
		antiplatelet and anticoagulation	3–15)[b]					Nosocomial	
2001–2003		therapy						pneumonia	
			-						
			No MV						
Reusser et al.	40	Neurosurgical admission for severe	TBI 30 (75)	57/97	Ranitidine	7 days	-	UGIB	Overt UGIB:
1990 [37]		acute intracranial lesion, and	TBI with	(59)	50 mg every 6/8 h				Bright red blood via NG tube,
	36.5	respiratory failure due to impaired	multiple		IV,	7 days	Median days to onset of	Endoscopic endpoints	melena or a decrease in hemoglobin
Switzerland	(range	neurologic condition with need of	systems	1 (2.5)	titrated to maintain		enteral feeding was 4.75		>2 g/dl within 24 h, associated with
	15–76)	>48 h of MV	trauma 7		gastric pH ≥ 4	-	days (0.75)	Gastric pH	a positive stool guaiac test or with
Single centre;			(17.5)	-					>100 ml of coffee-ground aspirates
Academic SICU	30	Age < 15 years, history of upper GI	ICH 3 (7.5)		No intervention			ICU mortality	
	(75)	surgery or PUD with current							Occult UGIB: positive slide test on
August		antiulcer treatment or overt UGIB	-					Acute hospital	three consecutive aspirates
1984–September								mortality	
1986			5 (range 3–10)						
			15 (7.4)						
			-						
Senapathi et al	56	TBI patients with GCS <10	TBI 56 (100)	0 (0)	Omeprazole	5 days	56 (100)	UGIB	Positive benzidine stick for occult
2019 [38]	44.85				40 mg every 12 h IV				bleeding
Indonesia	(16–86)	Allergy and contraindications to	-	-	plus 15 ml of	8 days	Enteral nutrition was	Gastric pH	
Single centre; −	42	administrations of H2RA or PPI,			sucralfate every 8 h		started on the second day		
	(75)	acute GI bleeding, contraindications	7 (range 3–10)	-		-	of treatment in ICU		
		for NG or OG tube insertion, burns	-		Ranitidine				
		(>30% of total body surface area),	-		50 mg every 12 h IV				
		major trauma with ISS > 16,			plus 15 ml of				
		coagulopathy, gastric malignancy,			sucralfate every 8 h				
		unstable hemodynamics							

a = number and percentage of patients not included in the analysis for the primary outcomes among all eligible patients due to loss to follow-up and other reasons (missing important data, sudden death, loss of eligibility after randomization).
b = these data include patients receiving sucralfate and were not included in our analysis.
c = these data include patients receiving sucralfate and were not included in our analysis; additionally, 2 patients were lost to follow up for secondary outcome analysis only (one in the placebo group, the other in the experimental group).
GCS = Glasgow Coma Score; MV = mechanical ventilation; LTFU = lost to follow up; ICU = intensive care unit; GI = gastrointestinal; SUP = stress ulcer prophylaxis; hr = hours; ICH = intracranial hemorrhage; TBI = traumatic brain injury; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage; SCI = spinal cord injury; IV = intravenous; NG = nasogastric; UGIB = upper gastrointestinal bleeding; SICU = surgical ICU; PUD = peptic ulcer disease; ADH = antidiuretic hormone; CNS = central nervous system; CVD = cerebrovascular disease; AP-II = Acute Physiologic Assessment and Chronic Health Evaluation II; H2RA = H2 receptor antagonist; CT = computed tomography; PPI = proton pump inhibitor; OG = orogastric.

age of patients was 36.5 years, and 295 patients were female (32%). A total of 7 studies provided data on GCS [14,26-28,34,36,37], with a reported median GCS of six. All patients were mechanically ventilated at baseline.

3.3. Primary outcome

3.3.1. Gastrointestinal bleeding

Gastrointestinal bleeding data were available for 11 trials [14,26-30,32,34-37]. The duration of follow-up of GI bleeding events ranged from 1 to 15 days. GIB events used different definitions across the 11 trials, with 3 reporting occult blood loss [28,34,37], 9 reporting overt GI bleeding (see Table 1 for study-specific definitions) [14,27,29,30,32,34-37], and 2 reporting clinically important bleeding, defined as endoscopic evidence of lesions resulting in significant hemodynamic instability, transfusion or surgery [26,28].

In neurocritical care patients, H2RAs resulted in a lower incidence of gastrointestinal bleeding compared to placebo or no prophylaxis (Risk ratio [RR] 0.42, 95% CI 0.30–0.58; $p < 0.001$; $I^2 = 3\%$; Fig. 3a). Comparing PPIs with placebo or no prophylaxis, PPIs were associated with a lower incidence of GIB (RR 0.37, 95% CI 0.23–0.59; p < 0.001; $I^2 = 0\%$). Comparing PPIs and H2RAs, no significant difference was observed on GIB risk (RR 0.53, 95% CI 0.26–1.06; $p = 0.07$; $I^2 = 0\%$). Visual inspection showed slight asymmetry at the bottom of the funnel plots (eFigure 1).

The results for each criterion and definition are examined separately in eFigure 2. For trials where comparison between definitions was possible, HRAs resulted in a lower incidence of GIB compared to placebo when either the definition of overt clinical bleeding or clinically important GIB were used. No benefit was conferred to H2RAs administration in occult bleeding risk as compared to placebo.

All trials were determined as having an overall high risk of bias (See Fig. 2). Of the 11 included trials reporting GIB events, 3 trials were assessed as having low risk of bias arising from the randomization process as a random allocation sequence was used and allocation was concealed [14,27,36], as compared to the trial assessed as high risk of bias where patients were randomized by month of admission (subjects were randomized to PPI and H2RA groups, respectively on even and odd months of the year) [26]. Seven trials were deemed as low risk of bias from intended intervention [14,26,29,32,34-36]. Of the four trials deemed to be at high risk from intended intervention [27,28,30,37], most commonly this quality assessment reflected failures in implementing the intervention or the lack of an appropriate analysis to estimate the effect of intervention adherence. Most trials reported complete [27,28] or nearly complete data outcome data [14,26,29,30,32,34,36]. In the trial by Reusser et al. [37] 57 (59%) of 97 subjects were lost to follow-up, and in the trial by Liu et al. [35], 19 (11%) of 184 subjects were lost to follow-up. These two trials were deemed at high risk of bias with respect to outcome data. All trials were deemed low risk of bias in the measurement of outcome and having some concerns with selection of reported result, either because a prespecified analysis plan was unavailable, or the trial did not provide a flow diagram of subjects' progress through phases of the trial [14,26-30,32,34-37] .

3.3.2. All-cause 30-day mortality

Data on mortality were available in 7 trials involving 474 patients [27,28,30,32,35-37]. The duration of follow-up ranged from 3 to 30 days, and the median time to final follow-up assessment for mortality was 22.5 days. There was no statistically significant difference in all-cause mortality in patients receiving H2RAs as compared to placebo or no prophylaxis (RR 0.77; 95% CI 0.55–1.07; $p = 0.12$; $I^2 = 0\%$) (Fig. 4). Limited data precluded analysis of any other comparisons.

All trials reporting on the outcome of 30-day mortality were determined as having an overall high risk of bias. Reasons for determination of trial quality were like the outcome of GIB.

3.3.3. ICU length of stay

Data on ICU length of stay was available in 2 trials involving 100 patients [34,37]. Limited data and differing comparators between the 2 studies precluded meta-analysis. Reusser et al. (1990) [37] report similar lengths of stay between patients receiving ranitidine ($n = 19$; mean ICU LOS, 18.0 days [SD, 8.5 days]) and those receiving no prophylaxis ($n = 21$; mean ICU LOS, 17.3 days [SD, 6.3 days]). In the study by Lee et al. (2014) [34], no significant difference in ICU length of stay was seen between esomeprazole ($n = 30$) and famotidine (n = 30) groups, 23.6 days (SD, 12.4 days) and 23.3 days (SD, 12.1 days) respectively ($p = 0.842$).

3.3.4. Nosocomial pneumonia

Data on nosocomial pneumonia was available in 5 trials involving 493 patients [14,28,34-36]. However, only three [14,28,34] of the 5 studies used explicit definitions of this outcome. The proportion of patients receiving SUP who developed nosocomial pneumonia varied between 3.4% and 36.7%. The incidence was not significantly different among patients receiving H2RAs and placebo or no prophylaxis (RR 1.12; 95% CI 0.66–1.91; $p = 0.68$; $p = 0.17$ for heterogeneity; $I^2 = 40\%$) or between PPIs compared to H2RAs (17% vs. 15%; RR 1.08; 95% CI 0.56–2.08; $p = 0.82$; $I^2 = 0\%$) (Fig. 5). As too few trials comparing PPIs to placebo, or no prophylaxis reported on the outcome of nosocomial pneumonia statistical aggregation for this comparison could not be made.

Similar for determination of trial quality for the outcome of GIB, all trials were determined as having an overall high risk of bias for the outcome of nosocomial pneumonia.

3.3.5. Other adverse events

Five of the 14 studies reported on adverse events related to medication administration. Four (80%) studies reported no adverse events related to SUP [27,28,31,35]. In the study by Brophy et al. (2010) [26], an event rate of 10% ($n = 5/51$) was reported for thrombocytopenia, however no further details were reported.

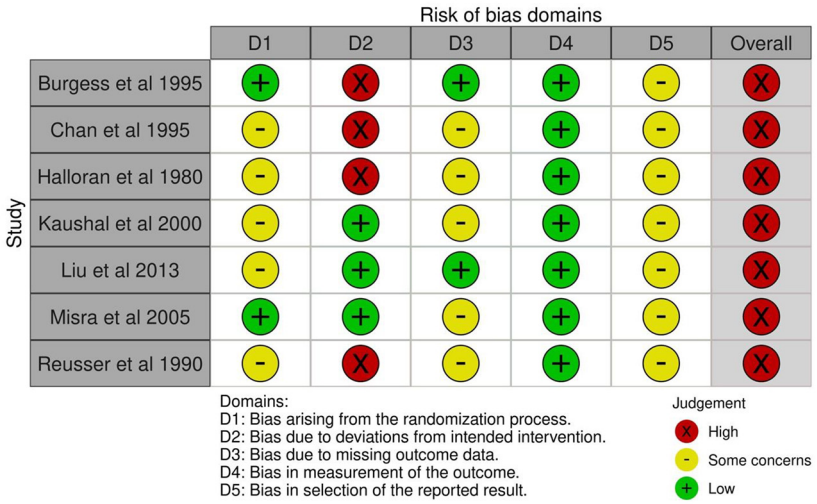
4. Discussion

This systematic review and meta-analysis suggest that SUP with either a H2RA or PPI is modestly more effective as compared to placebo or no prophylaxis in reducing GIB risk in ICU patients with a primary neurological injury. Further, no significant reduction is seen in all-cause 30-day mortality or did nosocomial pneumonia events increase. This differs from a prior meta-analysis showing SUP was more effective than placebo or no prophylaxis in reducing GI bleeding and all-cause mortality; the intervention groups were combined in this study, specifically both patients receiving either a H2RA or PPI were grouped together and compared to placebo or no prophylaxis [17].

Neurologic diagnoses account for approximately 1 in 5 admissions for critical care illness and constitute the third most prevalent admission category after cardiac and respiratory admissions [40]. In particular, ICH and cerebral infarction with major complications have been found to account for 64.6% of ICU utilization [41]. A well designed, large randomized controlled trial to determine prevalence of clinically important bleeding in a general neurocritical care patient population, as well as assessing risks within these neurocritical care subpopulations is needed. Neurocritical care patients are thought to be at increased risk of GIB due to several specific clinical risk factors. For instance, in a recent retrospective study involving 627 patients with SAH, of whom 61% were receiving pharmacologic prophylaxis against GIB, 4.9% of patients experienced clinically important GIB [42]. Reported risk factors for GIB in this study included increased ICP, reduce creatinine clearance (<60 ml/min) and incidence of cerebral vasospasm [42]. A higher prevalence of GIB of 8.4% has been reported in patients after an ischemic stroke [43]. Risk factors for GIB in this retrospective cohort study ($n = 1662$) included advanced age, high National Institute of Health Stroke Score,

a. UGIB

b. Acute hospital mortality



c. Hospital-acquired pneumonia

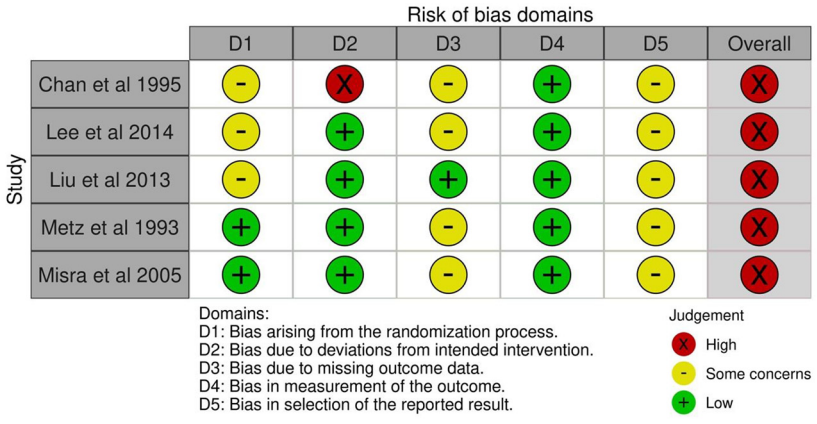


Fig. 2. Risk of bias summary of review authors' judgments about each risk of bias item for each included study. Green- low; yellow: - some concerns; red - high: risk of bias.

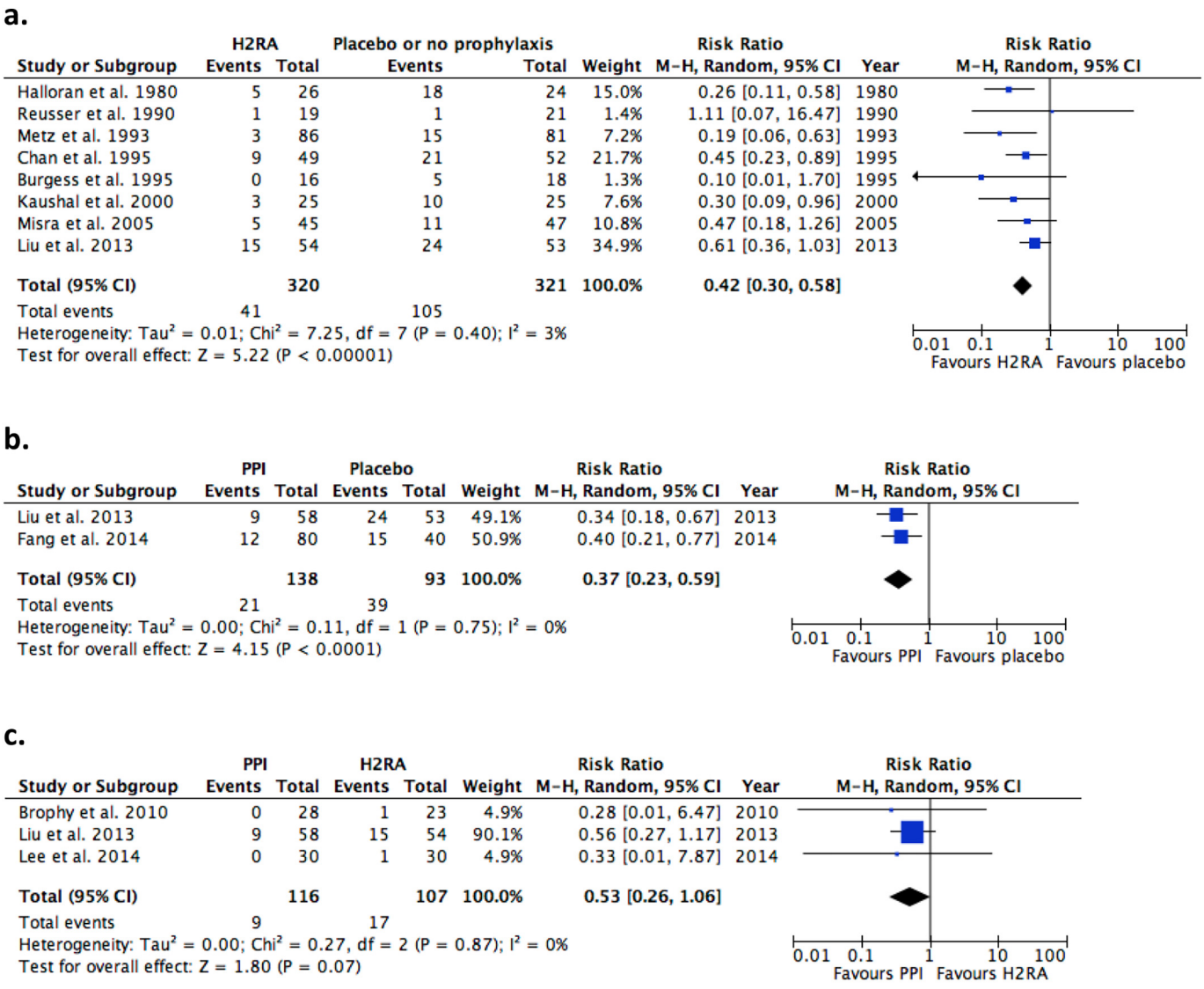


Fig. 3. Forest plot of stress ulcer prophylaxis (SUP) and gastrointestinal bleeding: (a) H2RA versus placebo or no prophylaxis, (b) PPI versus placebo, and (c) PPI versus H2RA. CI, confidence interval; M-H, Mantel-Haenszel method; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist.

depressed GCS, and posterior circulation infarction. We were unable to find studies regarding the prevalence and risk factors for GIB in a critically ill neuro-oncology population.

Patient-related benefits and harms of any intervention as compared to placebo or no prophylaxis as well as H2RAs as compared to PPIs requires rigorous evaluation. The reporting of enteral feeding practices in any future investigations is imperative to better understand underlying risk of clinically important bleeding in these patients [44]. A small number of trials were published after 2006, the year in which changes in enteral feeding practices were incorporated into existing clinical

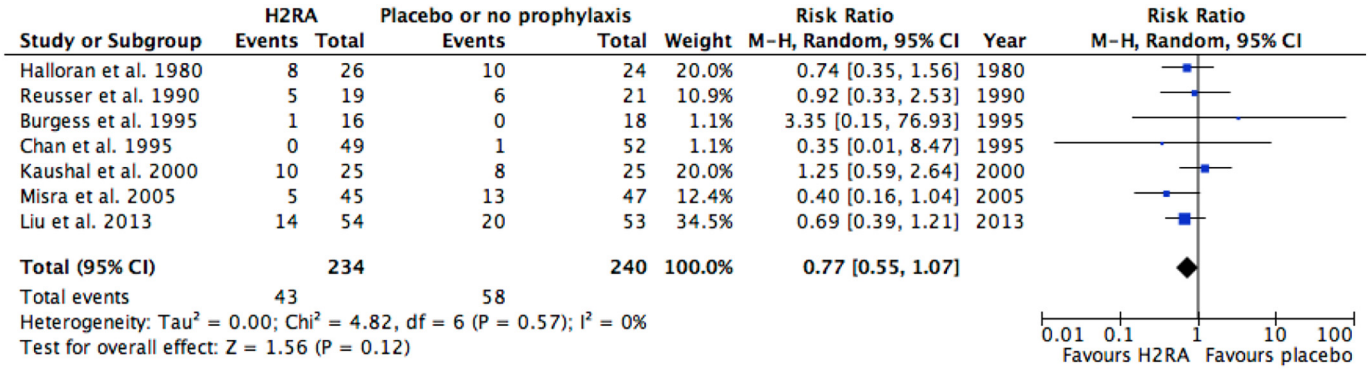


Fig. 4. Forest plot of stress ulcer prophylaxis, specifically H2RA versus placebo or no prophylaxis, and acute hospital/30-day mortality. CI, confidence interval; M-H, Mantel-Haenszel method; H2RA, H2 receptor antagonist.

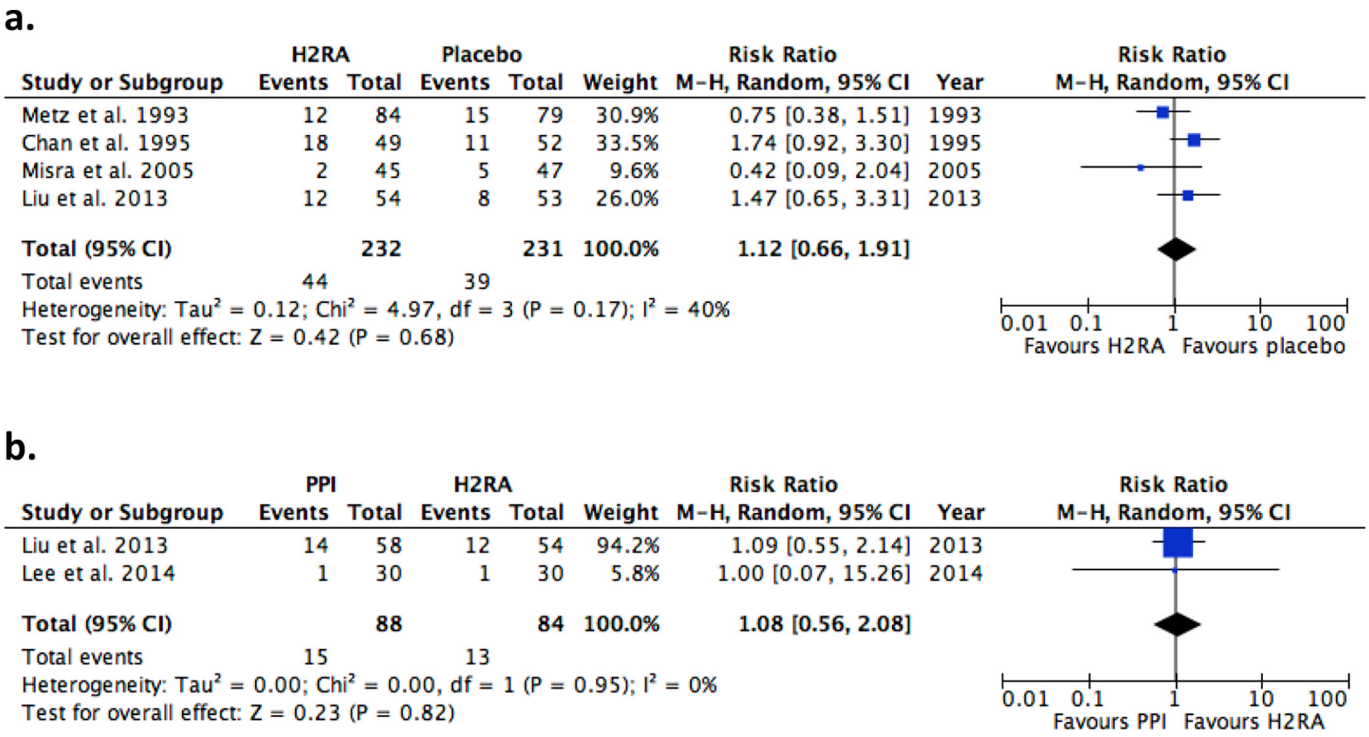


Fig. 5. Forest plot of stress ulcer prophylaxis and hospital acquired pneumonia: (a) H2RA versus placebo and (b) PPI versus H2RA. CI, confidence interval; M-H, Mantel-Haenszel method; PPI: proton pump inhibitor; H2RA, H2 receptor antagonist.

guidelines, limited our ability to make comparisons between unit feeding practices [45]. The highly variable timing of enteral nutrition in included trials further questions the importance of SUP especially as early enteral feeding becomes more common in critically ill adults [46,47]. We recognize, however, that feeding practices in critical care continue to evolve and impact patient outcomes [47-49]. Further trials are needed to clarify any benefits and harms in the context of early enteral nutrition and other current day neurocritical care practices.

A need for large, well-designed RCTs is warranted. Population enrichment with not only TBI and ICH patients, but also other acute neurological conditions such as spinal cord injury and aneurysmal subarachnoid hemorrhage should also be considered. An important consideration during trial design is defining of GIB as a primary outcome. Definitions of GIB vary in the literature, and as such depending on the GIB definition used investigators may over-, or alternatively, underestimate the incidence of clinically relevant GIB. Prior SUP studies most commonly have adopted the definition of clinically important bleeding. Clinically important bleeding is defined as overt bleeding in the absence of other causes with one of the following four features: 1) a spontaneous drop of systolic or diastolic blood pressure of >20 mmHg within 24 h of GIB, 2) an orthostatic increase in heart rate of 20 beats per minute and a decrease in systolic blood pressure of 10 mmHg, 3) a decrease in hemoglobin of >2 g/dl (20 g/l) in 24 h, or 4) transfusion of >2 units of packed red blood cells within 24 h of bleeding [50]. Other definitions of overt (e.g., hematemesis, coffee ground nasogastric aspirate, melena, etc.) or occult bleeding will lead to a higher prevalence of GIB that may not be clinically relevant. For example, having coffee ground nasogastric aspirate doesn't necessarily signify GIB, and if included as an outcome, could lead to overestimated GIB rates. Given the variable clinical importance of the definition used, we separated the included trials by definitions used prior to statistical aggregation to allow closer comparisons of similar outcomes studied. A limitation of our analysis is that there were a small number of events likely due to trial sizes being small. This review highlights the lack of high-quality evidence evaluating the influence of SUP in neurocritical care patients. These conclusions are analogous to those of a narrative review published recently discussing controversies regarding the use of SUP in neurocritical populations [51]. Importantly, this review also highlighted how the current literature is significantly limited in the lack of a uniformly adopted definition of GIB and the lack of large high-quality trials reflecting modern clinical practices.

Our review has other limitations. We are unable to make any strong conclusions as the included trials all demonstrate high risk of bias, sparse data is available on comparisons, significant heterogeneity exists between trials with regards to enrollment of patients with a primary neurological diagnosis (few trials focused exclusively on neurocritical care patients) as well as in medications prescribed in the intervention groups and comparator groups. Asymmetry of funnel plots support that our findings may have been influenced small study effects, including few events and limited data on specific patient characteristics (i.e., feeding practices). Strengths of this review however include rigorous methods to minimize bias, inclusion of a comprehensive literature search performed in collaboration with a medical librarian, duplicate data abstraction, consideration of important clinical outcomes, and use of an established process to assess study quality [20].

5. Conclusions

In neurocritical care patients, the overall high or unclear risk of bias of individual trials, the low event rates, and modest sample sizes preclude strong clinical inferences about the utility of SUP. Further trials are needed to clarify any benefits and harms in the context of early enteral nutrition and other current day neurocritical care practices.

Data availability statement

The original contributions presented in the study are included in the article and the appendices. Further inquiries can be directed to the corresponding author. Template data collection forms are publicly

available on Covidence (Version © 2022, Melbourne, Australia). The RoB2 excel tool is publicly available from the Cochrane Methods website.

Funding

This study received no funding.

Declaration of Competing Interest

The authors have no conflict of interests to report relevant to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154093.

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