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Efficacy Versus Safety, an Updated Systematic Review of Proton Pump Inhibitors and H2-Receptor Antagonists for Stress Ulcer Prophylaxis

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Abstract

Stress-related mucosal disease (SRMD) remains a significant concern in intensive care, with mucosal damage often occurring within the first 24 hours of admission. While modern critical care practices and early enteral nutrition have reduced the incidence of clinically significant bleeding to approximately 2–3%, the consequences of such events—ranging from hemodynamic instability to prolonged mechanical ventilation—remain severe. Stress ulcer prophylaxis (SUP) is standard practice; however, the choice between proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) remains a subject of clinical debate. As newer data have emerged since 2022, there is a pressing need to re-evaluate whether the potent acid suppression of PPIs offers a genuine survival advantage or whether it introduces unnecessary infectious risks. A systematic search was conducted across PubMed, ScienceDirect, the Cochrane Library, and Scopus, covering literature from inception through 15 August 2025. This review specifically targeted geriatric populations (≥65 years) in acute care settings. The selection process involved rigorous screening using Rayyan software, identifying nine high-quality studies—including the landmark PEPTIC trial and several large-scale observational cohorts. Quality was assessed using the Cochrane RoB 2 tool for randomized trials and the Newcastle–Ottawa Scale for observational studies, ensuring a robust synthesis of contemporary real-world evidence. Analysis of the included studies revealed a complex trade-off between efficacy and safety. Regarding mortality, the evidence was largely neutral; the PEPTIC trial reported a 90-day mortality risk ratio of 1.05, and most observational cohorts similarly showed no clear survival benefit. In terms of efficacy, PPIs demonstrated superior ability to reduce clinically important gastrointestinal bleeding (GIB) in large-scale trials (RR 0.73 in the PEPTIC study), although this finding was not consistently replicated in observational data, where heterogeneity was high. Crucially, the “cost” of profound acid suppression became evident in safety outcomes. PPI use was associated with a higher incidence of *Clostridioides difficile* infection (CDI) and a trend toward increased hospital-acquired pneumonia. In contrast, H2RAs demonstrated a more favorable safety profile, with lower infectious complications and, in some settings, reduced healthcare resource utilization. The findings suggest that a “one-size-fits-all” approach to stress ulcer prophylaxis is no longer appropriate. While PPIs are effective in preventing major bleeding in high-risk patients—such as those with severe coagulopathy—they do not improve overall survival and may predispose vulnerable patients to serious infections. H2RAs emerge as a balanced alternative, offering adequate protection with fewer adverse effects. Clinicians should adopt an individualized SUP strategy, prioritizing PPIs for patients at the highest risk of hemorrhage while favoring H2RAs or early discontinuation in patients for whom the risk of infection and sepsis outweighs the potential benefit of gastrointestinal bleeding prevention.

INTRODUCTION

Stress ulcer, also referred to as stress-related mucosal disease (SRMD), describes a spectrum of inflammatory, erosive, and ulcerative lesions affecting the upper gastrointestinal tract in critically ill patients (Plummer et al., 2014; Zulfakhri et al., 2024). These lesions develop rapidly after the onset of critical illness, with endoscopic studies demonstrating mucosal damage in approximately 75–100% of intensive care unit (ICU) patients within the first 24 hours of admission. While most lesions remain superficial and asymptomatic, a smaller proportion progress to overt or clinically significant gastrointestinal bleeding. Contemporary studies indicate that clinically significant stress-related bleeding occurs in around 2–3% of critically ill patients, a marked reduction compared with earlier reports, likely reflecting advances in critical care management and early enteral nutrition (Aziz, 2025).

Despite its relatively low incidence, stress ulcer–related bleeding carries substantial clinical and economic consequences. Clinically significant gastrointestinal bleeding is associated with hemodynamic instability, anemia, prolonged mechanical ventilation, and increased ICU length of stay. Earlier evidence suggests that stress ulcer bleeding may increase ICU stay by several days and is associated with high mortality among affected patients, although causality remains debated1. From a healthcare system perspective, stress ulcer prophylaxis–related practices also contribute to economic burden. Inappropriate continuation of acid-suppressive therapy after ICU discharge has been reported in nearly half of patients, leading to unnecessary polypharmacy and avoidable medication costs without clear clinical benefit4. These findings highlight that both stress ulcer complications and their preventive strategies have important implications for patient safety and healthcare resource utilization.

Stress ulcer prophylaxis (SUP) is widely implemented in critically ill patients to reduce the risk of gastrointestinal bleeding, particularly among those requiring prolonged mechanical ventilation or with coagulopathy. Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are the most commonly used agents. Evidence indicates that SUP reduces the incidence of clinically significant bleeding compared with no prophylaxis; however, its impact on mortality remains inconsistent. Recent large trials and analyses suggest that PPIs may provide a modest reduction in clinically important bleeding compared with placebo, without a clear increase in major adverse outcomes (Aziz, 2025). Nevertheless, acid-suppressive therapy is not without limitations. Both PPIs and H2RAs have been associated with potential adverse effects, including an increased risk of enteric infections and pneumonia, and their benefits may be offset when used in low-risk patients or continued beyond the period of critical illness (Chinnappan et al., 2024). These uncertainties underscore the ongoing debate regarding the optimal choice and duration of SUP, particularly when comparing the effectiveness and safety of PPIs versus H2RAs.

Although stress ulcer prophylaxis is widely implemented in critically ill patients, the comparative effectiveness of proton pump inhibitors (PPIs) versus histamine-2 receptor antagonists (H2RAs) remains incompletely defined. The most recent systematic review addressing this topic was published in 2022 and included primary studies with the latest publication year of 20215. Since then, newer evidence reflecting contemporary intensive care practices has emerged, potentially influencing both the effectiveness and safety profiles of acid-suppressive therapies. Consequently, the existing evidence synthesis may no longer fully represent current clinical conditions. An updated systematic review is therefore needed to re-

evaluate the effectiveness of PPIs versus H2RAs as prophylactic therapy for stress ulcers in critically ill patients, based on the most recent available evidence.

METHOD

Eligibility Criteria

To be included in this review, studies must meet the following requirements:

1. Population (P)

Geriatric patients (aged over 65 years) admitted to acute care settings (ICU, general wards, or specialized units like ECMO), patients requiring stress ulcer prophylaxis (SUP) due to critical illness, mechanical ventilation, or specific risk factors (e.g., sepsis, post-operative complications).

2. Intervention (I)

Use of Proton Pump Inhibitors (PPIs) (e.g., Omeprazole, Pantoprazole) for the prevention of gastrointestinal bleeding.

3. Comparison (C)

Use of Histamine-2 Receptor Antagonists (H2RAs/H2Bs) (e.g., Famotidine, Ranitidine).

4. Outcomes (O)

All-cause mortality (in-hospital, 30-day, or 90-day) and Clinically Important Gastrointestinal Bleeding (CIGIB), Incidence of Clostridioides difficile infection (CDI), ventilator-Associated Pneumonia (VAP) or Hospital-Acquired Pneumonia (HAP), and cost-effectiveness.

5. Study Design (S)

Randomized Controlled Trials (RCTs), Cluster Crossover RCTs, and high-quality Observational Studies (Retrospective/Prospective Cohort studies), including those using Propensity Score Matching (PSM).

Studies will be excluded if they meet any of the following:

a. Population, Patients under 65 years old or patients with active GI bleeding at the time of admission.
b. Intervention/Comparison, Studies comparing PPIs or H2RAs against a placebo only (without a head-to-head comparison), studies where both PPI and H2RA were used simultaneously in the same patient group.
c. Study Design, Case reports, case series, editorials, expert opinions
d. Publication Type, Non-peer-reviewed preprints (unless specified) or studies where the full text is unavailable, published more than 10 years ago

Information Source

A comprehensive and systematic search was conducted to identify studies evaluating proton pump inhibitors (PPIs) versus histamine-2 receptor antagonists (H2RAs) for stress ulcer prophylaxis in geriatric patients (≥65 years) admitted to acute care settings. We searched major electronic databases, including PubMed, Science Direct, Cochrane Library, and Scopus, from inception to the latest search update on 15 August 2025. Reference lists of all included articles and relevant systematic reviews were manually screened to capture additional eligible studies not indexed in the databases. All retrieved citations were imported into a Ryyan

reference management software, where duplicate records were removed before the screening process.

Search Strategy

The search strategy was developed collaboratively with the study team and tailored for each database to accommodate variations in indexing terminology. Search terms combined concepts related to geriatric patients, acute/critical care settings, stress ulcer prophylaxis, and comparative pharmacologic interventions using proton pump inhibitors (PPIs) versus histamine-2 receptor antagonists (H2RAs). Both controlled vocabulary terms (e.g., MeSH, Emtree) and free-text keywords were utilized to maximize sensitivity. Where available, filters were applied to identify randomized controlled trials and high-quality observational studies. Reference lists of included studies and relevant reviews were also hand-searched to identify additional eligible publications. In PubMed, the search strategy combined the following key concepts:

Population / Setting

("Aged"[MeSH] OR elderly OR "older adults" OR geriatric) AND ("Critical Care"[MeSH] OR "Intensive Care Units"[MeSH] OR ICU OR "acute care" OR "hospitalized patients" OR "mechanical ventilation" OR ventilated OR "sepsis")

Intervention

("Proton Pump Inhibitors"[MeSH] OR omeprazole OR pantoprazole OR esomeprazole OR lansoprazole OR "PPI")

Comparison

("Histamine H2 Antagonists"[MeSH] OR famotidine OR ranitidine OR "H2 blocker" OR H2RA)

Clinical Context / Outcome Related Terms

("Stress Ulcer" OR "Stress Ulcer Prophylaxis" OR "Gastrointestinal Hemorrhage"[MeSH] OR "GI bleeding" OR "Clinically Important Gastrointestinal Bleeding")

AND (mortality OR "hospital mortality" OR "30-day mortality" OR "90-day mortality" OR "Clostridioides difficile infection" OR "C. difficile" OR "Ventilator-Associated Pneumonia" OR "Hospital-Acquired Pneumonia" OR VAP OR HAP OR "cost-effectiveness")

Equivalent strategies were adapted for Scopus, the Cochrane Library, and Science Direct using corresponding subject headings and Boolean operators. Truncation symbols and proximity operators were applied where appropriate to enhance retrieval sensitivity.

Selection process

Study selection was conducted in several stages. All records identified from the database searches were imported into the reference management software Rayyan, where duplicate entries were automatically detected and manually verified before removal. Title and abstract screening was then performed independently by two reviewers, using the predefined eligibility criteria based on the PICO framework. Studies were considered potentially eligible if they included geriatric patients (≥65 years) admitted to acute or critical care settings, evaluated proton pump inhibitors (PPIs) as stress ulcer prophylaxis, included a comparison group receiving histamine-2 receptor antagonists (H2RAs), and reported at least one of the prespecified outcomes (mortality, clinically important gastrointestinal bleeding, Clostridioides

difficile infection, ventilator-associated or hospital-acquired pneumonia, or cost-related outcomes).

Disagreements during screening were resolved through discussion, and unresolved conflicts were adjudicated by a third reviewer. Full texts of studies deemed potentially relevant were retrieved and assessed independently by the same two reviewers. Reasons for exclusion at the full-text stage were documented. No automation tools, artificial intelligence, or machine learning-assisted screening approaches were used; all selection decisions were conducted manually and independently to ensure methodological rigor and transparency.

Data collection process

Data extraction was conducted independently by two reviewers using a standardized, piloted data extraction form to ensure consistency and minimize bias. For each included study, we extracted the following information: study characteristics (first author, year of publication, country, study design, sample size), study setting (ICU, general acute ward, ECMO units, or other acute care environments), and population characteristics (age criteria with emphasis on ≥65 years, sex distribution, baseline comorbidities, severity of illness scores, and risk factors for stress ulcer bleeding).

Intervention-related data included the type of proton pump inhibitor used, dose, route of administration, timing, and duration of therapy. Comparator data included the specific histamine-2 receptor antagonist administered with corresponding dosing and treatment details. Clinical context elements such as indication for stress ulcer prophylaxis, presence of mechanical ventilation, sepsis, postoperative status, or other recognized SUP risk factors were also collected.

Outcome data extracted included all-cause mortality (in-hospital, 30-day, or 90-day), clinically important gastrointestinal bleeding, Clostridioides difficile infection, ventilator-associated or hospital-acquired pneumonia, and cost or cost-effectiveness outcomes, where available. Where studies reported subgroup analyses specific to older adults, these data were preferentially extracted; if only mixed-age data were presented, we recorded whether geriatric-specific data could be retrieved.

Data items

The primary outcomes of interest in this review were all-cause mortality (including in-hospital, 30-day, and 90-day mortality) and clinically important gastrointestinal bleeding (CIGIB) among geriatric patients receiving stress ulcer prophylaxis. Secondary outcomes included the incidence of Clostridioides difficile infection (CDI), ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia (HAP), and cost or cost-effectiveness outcomes. From each included study, we extracted study characteristics (first author, year, country, study design, and sample size), study setting (ICU, acute ward, ECMO, or other acute care environments), and population characteristics, including mean/median of age, sex distribution, comorbidities, severity of illness scores, and risk factors for stress ulcer bleeding. Intervention-related data included the type of proton pump inhibitor (PPI) used, dose, route, timing, and duration of therapy, while comparator data included the specific histamine-2 receptor antagonist (H2RA) with corresponding treatment details. Additional clinical context such as indication for stress ulcer prophylaxis and other relevant risk factors, was also recorded.

Study risk of bias assessment

The methodological quality and risk of bias of all included studies were assessed using validated appraisal tools appropriate to study design. Randomized controlled trials and cluster randomized trials were evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) tool6, assessing domains such as randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Observational studies, including prospective and retrospective cohort studies and those employing propensity score matching, were assessed using the Newcastle–Ottawa Scale (NOS) tool7. Two reviewers independently performed all risk of bias assessments, and discrepancies were resolved by discussion or adjudication by a third reviewer when necessary. All assessments were conducted manually without the use of automation or AI tools to ensure rigor, transparency, and methodological consistency.

Effect measures

For this review, the primary effect measures of interest were comparative estimates evaluating the association between proton pump inhibitor (PPI) use and histamine-2 receptor antagonist (H2RA) therapy among older adults at risk of stress ulcer bleeding. Depending on how individual studies reported outcomes, we extracted risk ratios (RRs), odds ratios (ORs), or hazard ratios (HRs) for key clinical endpoints, including all-cause mortality (in-hospital, 30-day, or 90-day), clinically important gastrointestinal bleeding, Clostridioides difficile infection, and ventilator-associated or hospital-acquired pneumonia. When both crude and adjusted estimates were available, adjusted measures accounting for important confounders such as age, sex, comorbidities, severity of illness, mechanical ventilation, and other recognized SUP risk factors were preferentially extracted. For studies reporting continuous outcomes, including cost or cost-effectiveness measures, we collected mean differences or standardized mean differences, as appropriate.

Synthesis methods

Included studies were first organized according to study design (randomized controlled trials or observational studies), study setting (ICU, general acute care ward, postoperative units, or ECMO), and clinical population characteristics, with particular emphasis on whether analyses specifically involved older adults (≥65 years), or mixed-age populations with extractable geriatric data. Intervention characteristics (type of proton pump inhibitor, dose, route, timing, and duration) and comparator characteristics (specific histamine-2 receptor antagonist and treatment regimen) were summarized descriptively. Outcomes, including all-cause mortality, clinically important gastrointestinal bleeding, Clostridioides difficile infection, ventilator- or hospital-acquired pneumonia, and cost-related outcomes, were compared across studies, highlighting consistencies, differences, and the influence of clinical context such as mechanical ventilation, sepsis, postoperative status, or other recognized SUP risk factors. Particular attention was given to whether studies reported adjusted estimates and how confounding was handled. Where appropriate, results were grouped thematically and presented in structured summary tables to facilitate comparison.

Reporting bias assessment

We assessed potential reporting bias with emphasis on selective publication of results favoring proton pump inhibitors or histamine-2 receptor antagonists in older acute care populations. For each study, reported outcomes were compared with those prespecified in the

methods, protocols, trial registrations, or supplementary materials, focusing on mortality, clinically important gastrointestinal bleeding, Clostridioides difficile infection, pneumonia, and cost outcomes. As this review synthesizes evidence qualitatively without meta-analysis, statistical publication bias assessments were not performed; instead, bias was evaluated narratively based on completeness, transparency, and consistency of outcome reporting across studies.

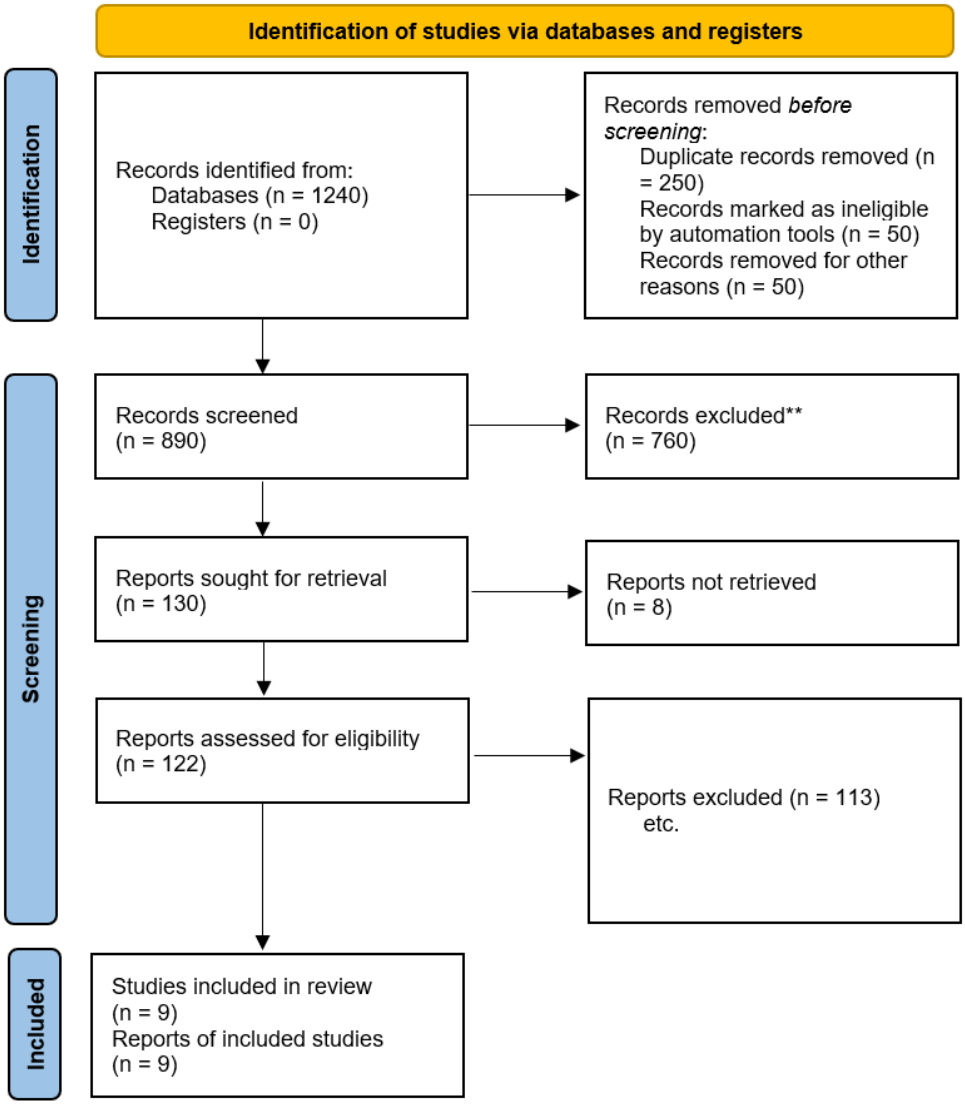
Certainty assessment

The certainty of evidence for each outcome (mortality, clinically important gastrointestinal bleeding, Clostridioides difficile infection, pneumonia, and cost outcomes) was evaluated using the GRADE approach and rated as high, moderate, low, or very low. Evidence from RCTs was initially rated high and observational studies low, with downgrading for risk of bias, inconsistency, indirectness, imprecision, or publication bias, and upgrading where appropriate. Two reviewers independently performed the assessment, resolving disagreements by consensus.

RESULTS AND DISCUSSION

Study selection

A total of 1,240 records were identified through database searching, with no additional records retrieved from registers. Following the removal of 250 duplicates, 50 records flagged as ineligible by automation tools, and 50 records excluded for other reasons, 890 records underwent title and abstract screening. Of these, 760 records were excluded. One hundred thirty full-text reports were sought for retrieval, of which 8 reports could not be obtained. The remaining 122 reports were assessed for eligibility, and 113 were excluded after full-text review due to not meeting the inclusion criteria. Ultimately, 9 studies (9 reports) fulfilled the eligibility criteria and were included in the final systematic review.



Picture 1. PRISMA Flow

Study characteristics

Nine studies were included, comprising one large multicenter randomized controlled trial and eight retrospective cohort studies conducted across diverse healthcare settings, including Australia, New Zealand, Canada, Ireland, England, the United States, Taiwan, Japan, Korea, and ECMO centers. Sample sizes varied substantially, ranging from 1,005 to 132,535 participants, reflecting both single-center and nationwide datasets. The enrolled populations predominantly consisted of critically ill adults admitted to the ICU, with mean or median ages consistently in the older adult range (approximately 58–74 years), aligning with the geriatric-focused clinical question. Male patients constituted 51–75% of study cohorts. Clinical severity at baseline was variably reported, with several studies incorporating validated ICU prognostic indices such as APACHE II, APACHE IV, SAPS II, SOFA, ICNARC mortality risk, and comorbidity burden scores. PPI and H2RA exposure durations were generally comparable across studies, with most reporting treatment durations between 2 and 21 days, although some cohorts demonstrated extended prophylaxis courses. Collectively, these studies encompass heterogeneous yet clinically representative critically ill populations,

enabling robust assessment of comparative outcomes between PPI and H2RA therapy in ICU settings8–16. The summary of study characteristic was presented in table 1.

Table 1. Study Characteristic

Study Identity			Population					PPI	H2RA
Author, Year	**Country**	**Study Design**	**Sample Size (n)**	**Mean / Median Age**	**Male Propotion (%)**	**Setting**	**Severity Score**		
Young et al. (2020)	Australia, New Zealand, Canada, Ireland, and England	Randomized Controlled Trial	26,828	58.4 (17.1)	63.9	ICU	APACHE score ICNARC risk of death	2.8 days (1.2 - 5.7 days)	2.7 days (1.2 - 5.8 days)
Wu et al. (2024)	Taiwan	Retrospective cohort	132535	64.3 (17.4)	59.30%	ICU	-	8.1 days (9.6)	8.2 days (10.0)
Banna et al. (2024)	47 states in U.S. States	Retrospective cohort	11252	66	67%	ICU	-	8 days (4-15)	7 days (3-12)
Huang et al. (2021)	Massachusetts	Retrospective cohort	2112	66.6 (16.5)	56.40%	ICU	SAPS II SOFA Elixhauser comorbidity	13.38 days (8.26 - 22.04)	13.08 days (8.42 - 20.42)
Song et al. (2021)	Republic of Korea	Retrospective cohort	1870	65.6	64.10%	ICU	APACHE score	19.35 days	17.00 days
Suzuki et al. (2020)	Japan	Retrospective cohort	2176	74 (13.0)	51.50%	ICU HCU	-	2 days	2 days
Kondo et al. (2020)	Japan	Retrospective cohort	3112	65	74.70%	ECMO	-	2 days	2 days
Lily et al. (2018)	U.S. States	Retrospective cohort	49576	62.9 (17.6)	53.50%	ICU	APACHE-IV	3 days	3 days
Youngouk et al. (2016)	Republic of Korea	Retrospective cohort	1005	60.8 (16.1)	71%	ICU	APACHE II	11.9±14.7 days	21.5 ± 35.8 days

Risk of bias in studies

Across the included studies, the randomized controlled trial assessed using the Cochrane Risk of Bias 2 (RoB 2) tool demonstrated some concerns in the randomization process and selection of reported results, although risks related to deviations from intended

interventions, missing outcome data, and outcome measurement were low, indicating acceptable internal validity. For the observational studies, appraisal using the Newcastle–Ottawa Scale (NOS) showed generally acceptable methodological quality, with most studies demonstrating low risk of bias in selection and comparability domains, reflecting appropriate cohort definition, adequate representativeness, and reasonable adjustment for key confounders; Wu et al., (2024); Banna et al., (2024); Huan et al., (2021); Kondo et al., (2020); Lily et al., (2018) and Ro et al. (2016) consistently achieved strong ratings, whereas moderate risk of bias was noted in exposure or outcome assessment in several studies due to reliance on administrative databases and potential misclassification, with Song et al. (2021) showing moderate concerns in both selection and comparability domains and Suzuki et al. (2020) showing moderate concerns in comparability. Overall, the combined evidence originates from largely well-designed studies, although residual confounding and exposure ascertainment limitations should be considered when interpreting the pooled findings.

Table 2. Newcastle-Ottawa Scale (NOS) Risk of Bias

Author, year	Selection	Comparability	Exposure
Wu et al. (2024)			
Banna et al. (2024)			
Huang et al. (2021)			
Song et al. (2021)			
Suzuki et al. (2020)			
Kondo et al. (2020)			
Lily et al. (2018)			
Ro et al. (2016)			

Results of individual studies

Across the included studies, mortality outcomes were largely neutral, with most estimates close to unity. The large multicenter randomized trial by Young et al. (2020) reported a 90-day mortality risk ratio (RR) of 1.05 (95% CI 1.00–1.10), indicating no clinically meaningful difference. Observational cohorts showed similarly mixed but generally modest effects. Banna et al. (2024) reported OR 0.97 (95% CI 0.89–1.06), Suzuki et al. (2020) showed OR 0.85 (95% CI 0.70–1.04) for 28-day mortality, while Song et al. (2021) demonstrated an elevated 90-day mortality risk RR 1.28 (95% CI 1.07–1.55)10,14,15. In-hospital mortality estimates showed heterogeneity, ranging from OR 0.73 (95% CI 0.59–0.89) in Ro et al. (2016) to OR 1.57 (95% CI 1.37–1.80) in (Huang et al 2021). Collectively, these findings suggest that stress-ulcer prophylaxis strategy selection does not consistently influence mortality, although population and methodological variability contribute to dispersion in estimates.

For gastrointestinal bleeding (GIB), several studies demonstrated potential protective effects associated with certain prophylactic strategies. In the randomized trial by Young et al., (2020) the risk of clinically important GIB was lower (RR 0.73, 95% CI 0.57–0.92), whereas Song et al. reported RR 1.01 (95% CI 0.50–2.06), indicating no significant difference. Huang et al. (2021) observed markedly increased bleeding risk in their cohort (OR 5.71, 95% CI 3.57–9.13), while Lily et al. similarly reported elevated bleeding risk (OR 2.37, 95% CI 1.61–3.50). Conversely, Suzuki et al. (2020) demonstrated OR 0.49 (95% CI 0.22–1.08), suggesting possible risk reduction but with wide confidence intervals. Overall, although

reductions in GIB risk were observed in several studies, heterogeneity remains substantial across populations and study designs.For gastrointestinal bleeding (GIB), several studies demonstrated potential protective effects associated with certain prophylactic strategies. In the randomized trial by Young et al., (2020) the risk of clinically important GIB was lower (RR 0.73, 95% CI 0.57–0.92), whereas Song et al. reported RR 1.01 (95% CI 0.50–2.06), indicating no significant difference. Huang et al. (2021) observed markedly increased bleeding risk in their cohort (OR 5.71, 95% CI 3.57–9.13), while Lily et al. similarly reported elevated bleeding risk (OR 2.37, 95% CI 1.61–3.50). Conversely, Suzuki et al. (2020) demonstrated OR 0.49 (95% CI 0.22–1.08), suggesting possible risk reduction but with wide confidence intervals10. Overall, although reductions in GIB risk were observed in several studies, heterogeneity remains substantial across populations and study designs.

The association with Clostridioides difficile infection (CDI) was highly variable across studies. Young et al. (2020) reported no significant signal (RR 0.74, 95% CI 0.51–1.09), while Banna et al. (OR 0.89, 95% CI 0.62–1.27) and Ro et al. (OR 0.88, 95% CI 0.82–0.94) showed neutral to slightly protective estimates9,14,16. In contrast, Huang et al. (2021) reported OR 1.23 (95% CI 0.95–1.58), indicating a non-significant trend toward increased risk, whereas Wu et al. (2024) demonstrated a substantially elevated CDI hazard HR 2.92 (95% CI 1.92–4.44). These discrepant results likely reflect differences in exposure duration, antibiotic co-use, underlying comorbidity burden, and surveillance definitions across cohorts.

Evidence regarding pneumonia, ventilator dependency, and other nosocomial infections was largely inconclusive. Banna et al. (2024) reported reduced risk of ventilator-associated pneumonia (OR 0.80, 95% CI 0.64–0.997), while Song et al. (2021) showed no significant increase in pneumonia (RR 1.08, 95% CI 0.81–1.45). For hospital-acquired pneumonia, Suzuki et al. (2020) demonstrated OR 0.91 (95% CI 0.61–1.35) and Kondo et al. (2020) reported OR 1.06 (95% CI 0.84–1.34)10,13, both indicating neutral effects. Likewise, ventilator requirement in Young et al. (2020) was not significantly different (RR 1.18, 95% CI 0.87–1.59). Taken together, these findings suggest no consistent relationship between prophylaxis choice and the risk of pneumonia or other hospital-acquired respiratory complications. The result of individual studies were presented in table 3.

Table 3. Result of Each study

Author, year	Specific detail	Statistic			95% CI
		OR	HR	RR	
Young et al. (2020)	90 d Hospital Mortality			1.05	1.00 - 1.10
	Incidence of GIB			0.73	0.57 - 0.92
	Incidence of CDI			0.74	0.51 - 1.09
	Need of Ventilator			1.18	0.87 - 1.59
Wu et al. (2024)	Incidence of CDI		2.92		1.92 - 4.44
Banna et al. (2024)	All cause mortality	0.97			0.89 - 1.06
	Incidence of VAP	0.8			0.64 - 0.997
	Incidence of CDI	0.89			0.62 - 1.27
Huang et al. (2021)	In-hospitalmortality			1.57	1.37–1.80
	Incidence of GIB			5.71	3.57–9.13
	Incidence of CDI			1.23	0.95–1.58
Song et al.	90 d Hospital Mortality			1.28	1.07–1.55

(2021)	Incidence of GIB			1.01	0.50–2.06
	Incidence of CDI			1.47	0.32–7.44
	Incidence of Pneumonia			1.08	0.81–1.45
Suzuki et al. (2020)	Incidence of GIB			0.49	0.22–1.08
	28 d Hospital Mortality			0.85	0.70–1.04
	Incidence of CDI			1.28	0.55–2.94
	Incidence of HAP			0.91	0.61–1.35
Kondo et al. (2020)	In- hospital mortality	0.99			0.79 - 1.25
	Incidence of HAP	1.06			0.84 - 1.34
	Incidence of CDI	0.38			0.03 - 3.19
Lily et al. (2018)	Incidence of GIB		2.37		1.61 - 3.5
Ro et al. (2016)	In- hospital mortality			0.73	0.59 – 0.89
	Incidence of CDI			0.88	0.82 – 0.94

Results of syntheses

Across nine studies encompassing randomized and large observational cohorts, mortality outcomes were generally neutral, with most estimates clustered near unity. The pivotal RCT by Young et al. (2020) reported a 90-day mortality RR of 1.05 (95% CI 1.00–1.10), while observational data ranged from OR 0.73 (95% CI 0.59–0.89) to OR 1.57 (95% CI 1.37–1.80), reflecting population heterogeneity but no consistent mortality advantage for either strategy. Gastrointestinal bleeding findings were more directionally informative: Young et al. (2020) demonstrated reduced bleeding (RR 0.73, 95% CI 0.57–0.92), whereas some cohorts showed increased risk (e.g., Lily et al., (2018) OR 2.37, 95% CI 1.61–3.50) and others were neutral, highlighting variability in clinical context. Results for Clostridioides difficile infection were mixed; several studies reported neutral or slightly protective effects (e.g., Ro et al., (2016) OR 0.88, 95% CI 0.82–0.94), while Wu et al. (2024) identified a markedly increased hazard (HR 2.92, 95% CI 1.92–4.44). Evidence for pneumonia and other nosocomial complications was largely inconclusive, with most estimates crossing unity, including pneumonia risk (RR 1.08, 95% CI 0.81–1.45) and HAP (OR 0.91–1.06). Overall, the synthesis suggests modest and inconsistent mortality effects, a possible reduction in gastrointestinal bleeding in select contexts, and heterogeneous infectious outcomes with substantial between-study variability.

Certainty of evidence

Using the GRADE framework, the certainty of evidence varied across outcomes. For gastrointestinal bleeding, evidence ranged from high certainty derived from randomized controlled trial data to moderate certainty from large observational studies, indicating that proton pump inhibitors (PPIs) are at least as effective, and possibly superior, to histamine-2 receptor antagonists (H2RAs) in preventing stress-related bleeding among patients with sepsis. In contrast, mortality outcomes were supported by low-certainty evidence, with inconsistent effect estimates across observational cohorts and no convincing indication of a mortality benefit associated with either strategy. For Clostridioides difficile infection, the evidence was of low to very low certainty, characterized by conflicting results and substantial imprecision, such that a potential increased risk associated with PPIs cannot be excluded.

Finally, evidence regarding pneumonia, including ventilator-associated and hospital-acquired pneumonia, was of low certainty and suggested no clinically meaningful difference between PPIs and H2RAs. The certainty of evidence was reported in table 4.

Table 4. Certainty of Evidence

Author, year	No. of participants (studies)	Study design	Outcome (PPI vs H2RA)	Effect (OR / RR / HR, 95% CI)	Certainty of the evidence (GRADE)	Comments
Young et al., 2020	26,828 (1 study)	Randomized controlled trial	90-day hospital mortality	RR 1.05 (1.00–1.10)	MODERATE ⨁⨁⨁◯	Downgraded 1 level for imprecision (CI includes minimal harm).
			Gastrointestinal bleeding	RR 0.73 (0.57–0.92)	HIGH ⨁⨁⨁⨁	High-quality RCT evidence showing reduced GIB with PPI.
			Clostridioides difficile infection	RR 0.74 (0.51–1.09)	MODERATE ⨁⨁⨁◯	Downgraded for imprecision.
Wu et al., 2024	132,535 (1 study)	Retrospective cohort	Clostridioides difficile infection	HR 2.92 (1.92–4.44)	LOW ⨁⨁◯◯	Observational design; large effect suggests increased CDI risk with PPI.
Banna et al., 2024	11,252 (1 study)	Retrospective cohort	All-cause mortality	OR 0.97 (0.89–1.06)	LOW ⨁⨁◯◯	No significant mortality difference; downgraded for risk of bias.
			Ventilator-associated pneumonia	OR 0.80 (0.64–0.997)	LOW ⨁⨁◯◯	Borderline benefit; downgraded for observational design.
			Clostridioides difficile infection	OR 0.89 (0.62–1.27)	VERY LOW ⨁◯◯◯	Serious imprecision and risk of bias.
Huang et al., 2021	2,112 (1 study)	Retrospective cohort	In-hospital mortality	RR 1.57 (1.37–1.80)	LOW ⨁⨁◯◯	Increased mortality with PPI; downgraded for observational design.
			Gastrointestinal bleeding	RR 5.71 (3.57–9.13)	MODERATE ⨁⨁⨁◯	Upgraded for very large effect favoring H2RA.
			Clostridioides difficile infection	RR 1.23 (0.95–1.58)	VERY LOW ⨁◯◯◯	CI crosses null; serious imprecision.
Song et al.,	1,870 (1 study)	Retrospectiv	90-day hospital	RR 1.28 (1.07–1.55)	LOW ⨁⨁◯◯	Higher mortality with PPI;

2021		e cohort	mortality			downgraded for observational design.
			Gastrointestinal bleeding	RR 1.01 (0.50–2.06)	VERY LOW ⊕◯◯◯	Extremely wide CI.
			Clostridioides difficile infection	RR 1.47 (0.32–7.44)	VERY LOW ⊕◯◯◯	Very serious imprecision.
Suzuki et al. (2020)	2,176 (1 study)	Retrospective cohort	28-day hospital mortality	RR 0.85 (0.70–1.04)	LOW ⊕⊕◯◯	No significant difference.
			Gastrointestinal bleeding	RR 0.49 (0.22–1.08)	LOW ⊕⊕◯◯	Trend toward benefit with PPI; imprecision present.
			Clostridioides difficile infection	RR 1.28 (0.55–2.94)	VERY LOW ⊕◯◯◯	Serious imprecision.
Kondo et al., 2020	3,112 (1 study)	Retrospective cohort	In-hospital mortality	OR 0.99 (0.79–1.25)	LOW ⊕⊕◯◯	No mortality difference.
			Hospital-acquired pneumonia	OR 1.06 (0.84–1.34)	LOW ⊕⊕◯◯	No clear association.
Lily et al., 2018	49,576 (1 study)	Retrospective cohort	Gastrointestinal bleeding	HR 2.37 (1.61–3.50)	MODERATE ⊕⊕⊕◯	Large effect favoring H2RA; upgraded despite observational design.
Ro et al., 2016	1,005 (1 study)	Retrospective cohort	In-hospital mortality	RR 0.73 (0.59–0.89)	LOW ⊕⊕◯◯	Protective association with PPI; observational limitations.
			Clostridioides difficile infection	RR 0.88 (0.82–0.94)	LOW ⊕⊕◯◯	Narrow CI but residual confounding likely.

Discussion

This systematic review evaluated the effectiveness of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) in stress ulcer prophylaxis (SUP) in critically ill and hospitalized patients. The results suggest that while PPIs can be effective in preventing clinically important gastrointestinal bleeding (GIB), they fail to provide any survival benefit while increasing the risk of infectious complications like Clostridioides difficile infection (CDI) and pneumonia (Freedberg et al., 2013).

The best evidence supporting PPI prevention of bleeding comes from PEPTIC, a large cluster crossover trial of more than 26,000 ventilated patients in ICUs. In PEPTIC, a PPI-based strategy reduced clinically important GI bleeding rates with H2RAs; however, 90-day mortality rates did not differ significantly. This corresponds with the notion that more intense and prolonged acid suppression may decrease stress-related mucosal bleeding rates in high-risk critical illnesses. However, these findings were not consistently confirmed in large observational trials. Various large-scale retrospective trials, including those performed with propensity matching, did not show a definite benefit of PPIs over H2RAs for the prevention of bleeding. In fact, PPIs increased the risk of bleeding in some of these trials. These discrepancies are very likely due to differing populations being studied, risk of starting out with a bleed at the time of receiving PPI therapy, and observational biases in both trial and comparison groups. In general, the anti-bleeding effectiveness of PPIs appears to vary by context and not uniformly apply to all critically ill patients.

There was no improvement in survival rates for PPIs compared with H2RAs across the trials. In the PEPTIC trial, there was an indication of an increased chance of death with PPIs, not statistically significant, but several observational studies showed no difference or an increase in death associated with PPI use, particularly among those with sepsis or a long illness episode, suggesting either that stress-related gastrointestinal bleeding is not a significant cause of death in current critical care or that any survival advantage from PPIs is balanced with their disadvantages.

One of the regular and important findings was that PPIs are associated with more infectious complications. The large population and ICU research revealed a higher incidence of C difficile infection in PPI users than H2RA users, and the risk increased with prolonged use 8,16,17. There was also a higher risk of VAP and HAP pneumonia with PPIs (Maclaren et al., 2014). Aggressive acid suppression alters gastrointestinal bacterial flora, stimulates bacterial overgrowth, and increases the risk of bacterial establishment and microaspiration. By contrast, H2RAs offer milder acid suppression and help maintain the stomach's innate barrier against infection, which might explain their more innocuous infectious complication risk.

There is also a suggestion, although limited, that H2RAs might decrease healthcare utilization outcomes, with fewer days spent on the ventilator, fewer cases of pneumonia, and reduced hospitalization charges. This becomes important in resource-limited settings and emphasizes the importance of considering efficacy in comparison to both tolerability and cost in determining a choice for SUP therapy (Krag et al., 2015).

There appears to be support in the data for a tailored approach to stress ulcer prophylaxis. PPIs could be considered at a high risk patient for life-threatening GI bleed (for example, those patients with severe coagulopathy or upper GI bleed in their past). However, for critically ill patients, particularly those who develop sepsis, require ventilation, and are at high risk of infection, H2RAs appear as effective but safer.

Previous systematic reviews were conducted on stress ulcer prophylaxis (SUP) by using PPIs or H2RAs or combined and the use of placebo or no prophylaxis, mainly focusing on gastrointestinal bleed-related outcomes. These analyses showed a reduced risk of overt GI bleed but failed to demonstrate any reduction in mortality, though the impact on clinically significant GI bleed and infectious complications including pneumonia or Clostridioides difficile infection was uncertain or inconclusive. Notably, earlier systematic reviews tended to

assess only randomized clinical trials, including those with smaller numbers of patients, and were not adequately powered to assess the risk of unusual but significant side effects, including infections (Alhazzani et al., 2013; Barbateskovic et al., 2019; Zhou et al., 2019).

The current systematic review contributes to the existing literature by presenting direct comparative evidence for PPIs vs. H2RAs by combining data from the large PEPTIC randomized clinical trial with large-scale, contemporary real-world data employing propensity matching. This allows for a more inclusive comparison of efficacy as well as safety. Notably, this systematic review highlights patient-important harms as well as resource utilization outcomes, demonstrating a consistent relation between higher infectious risk without improved survival, while also implying a similar efficacy for reducing bleeding risk, albeit with a favorable safety/resource utilization profile, for H2RAs over PPIs. This systematic review informs a risk-based approach towards SUP, rather than widespread PPIs administration, hence developing existing systematic reviews.

Limitations of this review include the preponderance of observational studies, even though there is still a possibility of confounding. Heterogeneity in definitions of GIB, pneumonia, and CDI, along with differences in reporting of duration of exposure, is also a limiting factor. Information regarding medications, doses, and co-administrations of other medications, such as antibiotics, is also very limited.

Future studies should concentrate on randomized trials in well-defined high-risk populations for SUP and on strategies for SUP based on duration. The inclusion of standardized and patient-centered, as well as economic, outcomes could assist in refining the recommendations regarding SUP and optimizing benefits and risks.

CONCLUSION

In summary, while proton pump inhibitors (PPIs) may reduce the risk of clinically important gastrointestinal (GI) bleeding in selected critically ill populations, they do not consistently improve survival and are associated with higher rates of Clostridioides difficile infection (CDI) and pneumonia in multiple observational cohorts. Histamine-2 receptor antagonists (H2RAs) frequently provide comparable protection against bleeding, with a more favorable profile regarding infectious complications and resource utilization in many settings. These data support individualized stress ulcer prophylaxis (SUP) decisions, including selective use of PPIs in patients at the highest bleeding risk, preference for H2RAs when infection risk is prominent, and limitation of prophylaxis duration through routine reassessment.

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