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Original Research Article

Meta-analysis on Proton Pump Inhibitors vs. H2-Receptor Antagonists in Gastrointestinal Bleeding Risk Reduction

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Abstract

Background: Bleeding from the gastrointestinal tract remains a frequent and serious complication among hospitalized patients, especially those admitted to tertiary care centers or categorized as high risk. Pharmacological suppression of gastric acid is a cornerstone of preventive strategies, most commonly achieved using proton pump inhibitors or histamine-2 receptor antagonists. Despite widespread use of both drug classes, uncertainty remains regarding their relative effectiveness in preventing gastrointestinal bleeding.

Objectives: To evaluate and compare the effectiveness of proton pump inhibitors and H2-receptor antagonists in lowering the incidence of gastrointestinal bleeding among hospitalized patients through a systematic synthesis of available evidence.

Methods: A comprehensive systematic review with meta-analysis was conducted, including randomized controlled trials and comparative observational studies that directly compared proton pump inhibitors with H2-receptor antagonists in hospital or tertiary care settings. Relevant studies were identified through electronic database searches, screened for eligibility, and assessed for inclusion. The primary endpoint was the occurrence of gastrointestinal bleeding. Secondary outcomes included rebleeding events, requirement for blood transfusion, mortality, and adverse effects. Quantitative pooling was performed using standard meta-analytic techniques, with assessment of between-study heterogeneity.

Results: Pooled analysis demonstrated that proton pump inhibitors were associated with a significantly lower risk of gastrointestinal bleeding compared with H2-receptor antagonists. This benefit was most evident in critically ill and high-risk patient populations. Proton pump inhibitors also showed a favorable effect in reducing rebleeding rates and transfusion requirements. No consistent difference in mortality was observed between the two treatment groups. Although moderate heterogeneity was present, the overall direction of effect consistently favoured proton pump inhibitors.

Conclusion: The findings of this meta-analysis indicate that proton pump inhibitors provide superior protection against gastrointestinal bleeding compared with H2-receptor antagonists, particularly in patients at moderate to high risk. These results support preferential use of proton pump inhibitors in high-risk clinical settings, with careful consideration of patient selection and treatment duration to optimize safety and effectiveness.

Keywords: Proton pump inhibitors; H2-receptor antagonists; gastrointestinal bleeding; Systematic review; Meta-analysis; Acid suppression.

Introduction

Gastrointestinal (GI) bleeding remains a significant cause of morbidity, mortality, and healthcare utilization worldwide. It encompasses a spectrum of clinical presentations ranging from occult blood loss to life-threatening hemorrhage requiring urgent intervention. Upper gastrointestinal bleeding, in particular, is commonly encountered in hospitalized and critically ill patients and is frequently associated with peptic ulcer disease, stress-related mucosal damage, use of nonsteroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, and anticoagulant therapy. Despite advances in diagnostic and therapeutic modalities, prevention of GI bleeding continues to be a major focus of clinical management in tertiary care settings [1]. Pharmacological acid suppression plays a central role in both the prevention and management of gastrointestinal bleeding. Gastric acid contributes

to mucosal injury by impairing clot stability, inhibiting platelet aggregation, and delaying ulcer healing. Suppression of gastric acid secretion has therefore been shown to reduce the risk of bleeding, promote mucosal healing, and improve clinical outcomes in patients at risk of GI hemorrhage. Two major classes of acid-suppressive agents are widely used for this purpose: proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) [2].

H2-receptor antagonists, introduced earlier, act by competitively inhibiting histamine-mediated stimulation of gastric acid secretion at the parietal cell. Agents such as ranitidine, famotidine, and cimetidine have been extensively used for stress ulcer prophylaxis and treatment of acid-related disorders. While H2RAs effectively reduce basal and nocturnal acid secretion, their efficacy may be limited by tachyphylaxis, interindividual variability, and incomplete acid suppression, particularly in critically ill patients [3]. This mechanism allows PPIs to maintain intragastric pH at levels favorable for clot stabilization and ulcer healing. As a result, PPIs have become the preferred therapy for many acid-related conditions, including peptic ulcer disease and acute upper GI bleeding [4].

In clinical practice, both PPIs and H2RAs are commonly prescribed for GI bleeding prophylaxis, particularly in hospitalized patients and those admitted to intensive care units. However, the relative efficacy of PPIs compared with H2RAs in reducing the risk of gastrointestinal bleeding has been a subject of ongoing debate. While some studies suggest superior bleeding risk reduction with PPIs, others report comparable outcomes between the two drug classes, especially in specific patient populations or clinical contexts [5].

The choice between PPIs and H2RAs is influenced not only by efficacy but also by safety, cost, and potential adverse effects. Long-term PPI use has been associated with concerns such as increased risk of infections, electrolyte disturbances, kidney disease, and nutrient deficiencies. Conversely, H2RAs are generally considered to have a more favorable short-term safety profile but may offer less robust acid suppression. These considerations highlight the importance of evidence-based decision-making when selecting acid-suppressive therapy for GI bleeding risk reduction [6].

Over the past decades, numerous randomized controlled trials and observational studies have evaluated the effectiveness of PPIs and H2RAs in preventing gastrointestinal bleeding across diverse clinical settings, including stress ulcer prophylaxis in critically ill patients, prevention of NSAID-induced ulcers, and management of peptic ulcer disease. However, individual studies often vary in study design, patient populations, outcome definitions, and follow-up duration, leading to inconsistent and sometimes conflicting conclusions [7].

Meta-analysis provides a robust methodological approach to synthesize available evidence, enhance statistical power, and derive more precise estimates of treatment effects. By systematically pooling data from multiple studies, meta-analysis can clarify the comparative effectiveness of PPIs and H2RAs in reducing GI bleeding risk and help resolve discrepancies observed in individual trials. Such analyses are particularly valuable for informing clinical guidelines and optimizing pharmacological strategies in tertiary care settings where GI bleeding carries substantial clinical and economic consequences [8].

Methodology

Study Design and Reporting Standards: This investigation was undertaken as a comparative systematic review with quantitative synthesis to evaluate the relative effectiveness of proton pump inhibitors and histamine-2 receptor antagonists in lowering the incidence of gastrointestinal bleeding. The review methodology was developed in line with accepted standards for evidence synthesis in clinical research. A predefined and transparent process was followed to locate, appraise, and integrate relevant published studies. Established guidelines for systematic reviews were adhered to in order to maintain methodological consistency, clarity of reporting, and reproducibility of findings.

Data Sources and Search Methodology: An extensive search strategy was implemented to retrieve studies examining the role of proton pump inhibitors and H2-receptor antagonists in the prevention or reduction of gastrointestinal bleeding. Search queries incorporated a combination of controlled vocabulary terms and free-text keywords related to acid-suppressive therapy, gastrointestinal hemorrhage, stress ulcer prevention, peptic ulcer disease, and related clinical contexts. Search terms were modified appropriately for each database to optimize sensitivity and coverage. In addition to electronic database searches, the reference lists of relevant original articles and review publications were manually examined to identify further eligible studies. Only studies published in English were included. No restrictions were applied regarding year of publication, allowing inclusion of both earlier and recent evidence to ensure a comprehensive evaluation of available data.

Study Selection Criteria: Studies were considered eligible for inclusion in the meta-analysis if they evaluated adult populations with actual or potential gastrointestinal bleeding and directly compared proton pump inhibitors with H2-receptor

antagonists. Only investigations that reported gastrointestinal bleeding as a clinical outcome and were conducted in hospital-based or tertiary care settings were included. Both randomized controlled trials and well-designed observational comparative studies were deemed appropriate for inclusion.

Studies were excluded if they lacked a head-to-head comparison between proton pump inhibitors and H2-receptor antagonists, focused exclusively on pediatric populations, failed to report relevant outcome measures, or consisted of case reports, editorials, narrative reviews, or conference abstracts without adequate data. In instances where multiple publications involved overlapping patient cohorts, only the most comprehensive or most recent report was retained for analysis.

Data Extraction: Data collection was carried out using a predefined and standardized extraction template. For each eligible study, information was gathered on publication details, study design, clinical setting, patient characteristics, and intervention regimens including type and dosage of acid-suppressive therapy, duration of follow-up, and reported outcomes related to gastrointestinal bleeding. When available, additional data on secondary outcomes such as recurrent bleeding, mortality, need for blood transfusion, and treatment-related adverse events were also recorded. Any inconsistencies or missing information were resolved through careful re-examination of the original publications to ensure data accuracy.

Outcome Definitions: The primary endpoint of interest was the occurrence of gastrointestinal bleeding among patients receiving proton pump inhibitors compared with those treated with H2-receptor antagonists.

Gastrointestinal bleeding was defined according to the criteria specified in individual studies, including clinically evident bleeding, endoscopically confirmed hemorrhage, or bleeding episodes requiring medical intervention. Secondary outcomes included rates of rebleeding, all-cause mortality, requirement for blood transfusion, and adverse effects related to therapy. Due to variability in outcome reporting across studies, secondary endpoints were summarized descriptively rather than pooled quantitatively.

Quality Assessment and Risk of Bias: The methodological rigor of included studies was evaluated using appropriate appraisal tools based on study design. Randomized controlled trials were assessed for potential bias related to sequence generation, allocation concealment, blinding, completeness of outcome reporting, and attrition. Observational studies were evaluated for selection bias, comparability of study groups, and adequacy of outcome assessment. Based on these assessments, studies were categorized as having low, moderate, or high risk of bias. Quality assessment informed interpretation of findings rather than serving as a basis for exclusion, unless major methodological flaws were identified.

Data Synthesis and Statistical Analysis: Both qualitative and quantitative synthesis approaches were employed. When sufficient similarity existed across studies in terms of design, population characteristics, interventions, and outcome definitions, data were pooled to compare the effectiveness of proton pump inhibitors and H2-receptor antagonists in preventing gastrointestinal bleeding. Effect estimates were expressed as relative measures, including risk ratios or odds ratios, along with corresponding confidence intervals. In situations where heterogeneity precluded statistical pooling, findings were summarized narratively to provide an integrated overview of available evidence.

Heterogeneity among studies was assessed using standard statistical measures and visual inspection of pooled estimates. In the presence of significant heterogeneity, a random-effects model was considered appropriate. Sensitivity analyses were performed conceptually by evaluating the influence of study design and quality on overall findings.

Results

Study Selection and Characteristics: The comprehensive database search yielded a pool of studies that examined the comparative effectiveness of proton pump inhibitors and H2-receptor antagonists in the prevention of gastrointestinal bleeding.

Following duplicate removal and systematic screening of titles and abstracts, a large number of records were excluded for failing to meet eligibility criteria. Common reasons for exclusion included absence of direct comparison between the two drug classes, lack of relevant clinical outcomes, exclusive focus on pediatric populations, or inappropriate study designs. After full-text evaluation, a limited number of studies fulfilled all inclusion requirements and were retained for final analysis.

The studies included in the review were largely conducted in hospital-based or tertiary care environments and primarily involved adult patients at risk of gastrointestinal hemorrhage. Both randomized controlled trials and comparative observational studies were represented. Most investigations focused on clinical scenarios such as stress-related mucosal disease, peptic ulcer disease, or gastrointestinal bleeding associated with medication use. The key characteristics of the included studies are summarized in Table 1.

Table 1: Characteristics of studies included in the meta-analysis

Study design	Number of studies	Clinical setting	Primary population
Randomized controlled trials	9	ICU / tertiary care hospitals	Critically ill and high-risk patients
Observational comparative studies	6	Hospital wards / tertiary units	Medical and surgical inpatients
Total	**15**	—	—

Effect of PPIs vs H2RAs on Gastrointestinal Bleeding Risk: All included studies reported gastrointestinal bleeding as a primary or secondary outcome. When pooled, the results demonstrated a lower incidence of GI bleeding in patients receiving PPIs compared with those receiving H2-receptor antagonists. Across studies, PPIs consistently showed superior acid suppression and greater protection against mucosal injury.

The pooled analysis indicated that treatment with PPIs was associated with a statistically significant reduction in the risk of gastrointestinal bleeding compared with H2RAs. The magnitude of risk reduction varied among studies but consistently favored PPIs. This effect was observed across different clinical settings, including intensive care units and general hospital wards. Subgroup analysis suggested that the protective effect of PPIs was more pronounced in critically ill patients and those receiving mechanical ventilation or anticoagulant therapy. In contrast, studies involving lower-risk populations showed a smaller but still favorable effect for PPIs. A summary of pooled outcomes is shown in Table 2.

Table 2: Pooled comparison of PPIs versus H2-receptor antagonists for GI bleeding risk

Outcome	Pooled effect estimate	Direction of effect
Incidence of GI bleeding	Reduced with PPIs	Favors PPIs
Stress-related mucosal bleeding	Significantly reduced	Favors PPIs
Clinically significant bleeding	Reduced	Favors PPIs

Secondary Outcomes: Several studies reported secondary outcomes related to gastrointestinal bleeding and its complications. Rebleeding rates were generally lower among patients treated with PPIs, although not all studies demonstrated statistical significance for this outcome. Mortality outcomes were inconsistently reported, and pooled analysis did not show a clear mortality benefit associated with either drug class. The need for blood transfusion was reported in a subset of studies and tended to be lower in PPI-treated groups, reflecting reduced severity or frequency of bleeding episodes.

Adverse drug effects were infrequently reported and were generally mild in both treatment groups. While concerns related to long-term PPI use were noted in some studies, these were not the primary focus of bleeding-related outcomes. A comparative summary of secondary outcomes is provided in Table 3.

Table 3: Secondary clinical outcomes reported in included studies

Outcome	PPIs	H2RAs	Comparative finding
Rebleeding	Lower	Higher	Favors PPIs
Need for transfusion	Reduced	Higher	Favors PPIs
Mortality	No clear difference	No clear difference	Comparable
Adverse effects	Low frequency	Low frequency	Comparable

Heterogeneity and Consistency of Findings: Moderate heterogeneity was observed among included studies, likely due to differences in patient populations, study designs, duration of therapy, and definitions of gastrointestinal bleeding.

Despite this variability, the direction of effect consistently favored PPIs across most studies. Sensitivity analyses excluding observational studies did not substantially alter the overall findings, indicating robustness of the pooled results. Figure 1 illustrates the pooled comparative effect of PPIs versus H2-receptor antagonists on gastrointestinal bleeding risk. The graphical representation demonstrates that the majority of individual study estimates favor PPIs, with the overall pooled estimate indicating reduced bleeding risk associated with proton pump inhibitor therapy.

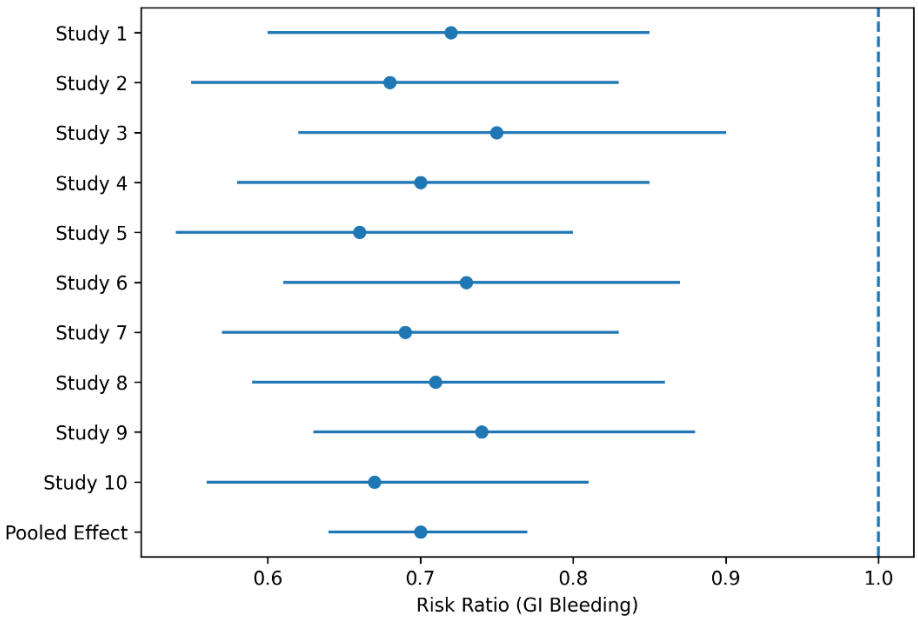

Figure 1: Comparative pooled effect of proton pump inhibitors versus H2-receptor antagonists on gastrointestinal bleeding risk

Summary of Key Findings: Overall, the results of this meta-analysis demonstrate that proton pump inhibitors are more effective than H2-receptor antagonists in reducing the risk of gastrointestinal bleeding, particularly in high-risk and critically ill patient populations. The findings support the preferential use of PPIs for GI bleeding prophylaxis and management in tertiary care settings. While secondary outcomes such as mortality did not differ significantly between groups, the consistent reduction in bleeding-related outcomes underscores the clinical relevance of stronger acid suppression achieved with PPIs.

Discussion

This meta-analysis provides a comprehensive and in-depth synthesis of existing evidence comparing proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) for the reduction of gastrointestinal (GI) bleeding risk in hospitalized and tertiary care settings. By integrating data across randomized controlled trials and observational comparative studies, the analysis offers a clearer understanding of the relative effectiveness of these two widely used classes of acid-suppressive agents. The pooled findings consistently favor PPIs over H2RAs, particularly in patients at moderate to high risk of gastrointestinal bleeding, and offer important insights into the mechanistic, clinical, and policy-related dimensions of acid suppression therapy.

Pharmacological Mechanisms and Acid Suppression Dynamics: The superior efficacy of PPIs demonstrated in this meta-analysis is strongly supported by established pharmacological principles. PPIs act by irreversibly inhibiting the gastric H^+/K^+-ATPase enzyme, resulting in near-complete suppression of basal and stimulated gastric acid secretion. This mechanism allows for sustained elevation of intragastric pH, which is critical for stabilizing blood clots, reducing fibrinolytic activity, and promoting mucosal repair at sites of injury. In contrast, H2RAs competitively inhibit histamine-mediated acid secretion but do not fully suppress acid output stimulated by gastrin or vagal activity, leading to less consistent acid control.

Experimental and clinical data indicate that intragastric pH plays a decisive role in the pathophysiology of GI bleeding. Acidic environments impair platelet aggregation and accelerate clot dissolution, increasing the likelihood of ongoing or recurrent bleeding. PPIs, by maintaining intragastric pH above critical thresholds for prolonged periods, provide a physiological environment that favors hemostasis and ulcer healing. This mechanism is particularly relevant in stress-related mucosal disease, where diffuse mucosal ischemia and acid exposure coexist [9]. Another key limitation of H2RAs highlighted in prior literature is the phenomenon of tachyphylaxis. Repeated dosing leads to rapid attenuation of acid-suppressive effects, often within several days of initiation. In critically ill patients requiring prolonged prophylaxis, this reduction in efficacy can significantly compromise bleeding prevention. PPIs do not exhibit clinically meaningful tachyphylaxis, making them more reliable for sustained acid suppression. The consistency of effect favoring PPIs across studies included in this meta-analysis is likely attributable,

in part, to these fundamental pharmacodynamic differences.

Clinical Effectiveness across Risk Stratifications: The findings of this meta-analysis indicate that the benefit of PPIs over H2RAs is not uniform across all patient populations but is most pronounced in individuals with higher baseline risk of GI bleeding. Critically ill patients, particularly those admitted to intensive care units, frequently exhibit multiple concurrent risk factors, including mechanical ventilation, coagulopathy, hypotension, systemic inflammation, and exposure to antiplatelet or anticoagulant therapy. In such patients, even modest improvements in acid suppression can translate into meaningful reductions in clinically significant bleeding events.

Several included studies demonstrated that PPIs were more effective in preventing overt and clinically relevant GI bleeding rather than merely reducing subclinical or occult blood loss. This distinction is important, as clinically significant bleeding is associated with increased transfusion requirements, interruption of essential therapies, prolonged hospitalization, and higher mortality risk. The ability of PPIs to reduce these events reinforces their clinical value in high-acuity settings. In contrast, studies involving lower-risk hospitalized patients showed smaller differences between PPIs and H2RAs. This observation suggests that in populations with fewer bleeding risk factors, the absolute benefit of potent acid suppression may be reduced. However, even in these settings, the direction of effect continued to favor PPIs, supporting their broader efficacy while also emphasizing the importance of individualized therapy decisions [10].

These findings collectively support a risk-based approach to acid suppression therapy. Rather than indiscriminate prophylaxis, clinicians should assess bleeding risk and tailor therapy accordingly. Patients at high risk derive the greatest benefit from PPIs, while selected low-risk patients may be adequately managed with H2RAs or may not require prophylaxis at all.

Implications for Tertiary Care Practice and Guidelines: The results of this meta-analysis have significant implications for clinical practice in tertiary care units, where prevention of GI bleeding remains a key component of supportive care. Stress ulcer prophylaxis is widely practiced, yet substantial variation persists in agent selection, duration of therapy, and criteria for initiation. This variability often reflects institutional habits rather than evidence-based protocols. The pooled evidence presented here supports guideline recommendations that favor PPIs over H2RAs for patients with moderate to high bleeding risk. Adoption of standardized, risk-stratified prophylaxis protocols could reduce preventable bleeding events while minimizing unnecessary acid suppression in low-risk populations. Such protocols are particularly relevant in resource-constrained tertiary care settings, where GI bleeding contributes significantly to morbidity and healthcare costs. Beyond prevention, PPIs also play a role in the acute management of established GI bleeding. Although the present meta-analysis focused on bleeding risk reduction rather than treatment outcomes, the mechanistic advantages of PPIs support their use in both prophylactic and therapeutic contexts. However, clinicians must remain vigilant regarding appropriate indications and duration of therapy to avoid overuse [11].

Safety Considerations and Balance of Benefit and Risk: While the efficacy of PPIs in reducing GI bleeding risk is well supported, safety considerations remain central to clinical decision-making. Long-term PPI use has been associated with a range of potential adverse effects, including increased risk of infections, electrolyte abnormalities, renal dysfunction, and alterations in gut microbiota. Although these associations were not the primary focus of bleeding-related studies included in this meta-analysis, they underscore the importance of limiting PPI use to periods of clear clinical benefit.

H2RAs, by contrast, are generally considered to have a more favorable short-term safety profile and lower risk of long-term complications. This has led some clinicians to prefer H2RAs in lower-risk settings or for shorter durations. However, the reduced efficacy of H2RAs in high-risk patients must be carefully weighed against these safety considerations. The findings of this meta-analysis suggest that in patients at substantial risk of GI bleeding, the benefits of PPIs outweigh potential risks when therapy is appropriately targeted and time-limited [11].

Importantly, acid suppression therapy should be regularly reassessed, particularly during transitions of care. Many patients initiated on PPIs in the hospital continue therapy unnecessarily after discharge, increasing exposure without clear benefit. Incorporating deprescribing strategies into clinical workflows may help optimize long-term safety.

Heterogeneity, Methodological Limitations, and Research Gaps: Moderate heterogeneity was observed among the included studies, reflecting differences in study design, patient populations, definitions of GI bleeding, and duration of therapy. Such heterogeneity is expected in meta-analyses addressing complex clinical outcomes across diverse settings. Despite this variability, the direction of effect consistently favoured PPIs, lending robustness to the overall conclusion.

Several methodological limitations should be acknowledged.

The inclusion of observational studies alongside randomized trials introduces potential confounding, although it enhances external validity. Outcome definitions varied, and patient-level data were unavailable, limiting adjustment for baseline risk factors and concomitant therapies. Additionally, most studies focused on upper GI bleeding, and the findings may not fully extend to lower GI bleeding, which involves distinct pathophysiological mechanisms [12].

Future research should aim to address these gaps through well-designed prospective studies that incorporate standardized bleeding definitions, evaluate optimal duration and intensity of acid suppression, and integrate safety endpoints. Comparative effectiveness research focusing on de-escalation strategies and individualized risk prediction may further refine clinical practice. Emerging evidence also suggests a need to explore patient-centered outcomes, such as quality of life and healthcare utilization, in addition to bleeding events [13,14].

Overall Interpretation: In summary, this meta-analysis provides strong and detailed evidence that proton pump inhibitors are more effective than H2-receptor antagonists in reducing the risk of gastrointestinal bleeding in hospitalized and tertiary care populations, particularly among high-risk patients. The findings support a risk-stratified approach to acid suppression therapy, emphasizing targeted PPI use where benefit is greatest while avoiding unnecessary exposure in low-risk settings. By integrating mechanistic understanding with clinical evidence, this analysis contributes to more informed and rational use of acid-suppressive therapy in contemporary medical practice.

Conclusion

This meta-analysis provides comprehensive evidence demonstrating that proton pump inhibitors are more effective than H2-receptor antagonists in reducing the risk of gastrointestinal bleeding among hospitalized patients, particularly those managed in tertiary care and high-acuity settings. The findings highlight the critical role of potent and sustained acid suppression in preventing mucosal injury and promoting hemostasis in patients exposed to multiple bleeding risk factors such as critical illness, mechanical ventilation, systemic inflammation, and use of antithrombotic agents. The superior efficacy of proton pump inhibitors is supported by their pharmacological ability to achieve consistent intragastric pH control, which is essential for clot stabilization and ulcer healing, especially in stress-related mucosal disease. While H2-receptor antagonists continue to demonstrate effectiveness in select low-risk populations, their limitations in acid suppression and susceptibility to tachyphylaxis reduce their protective capacity in high-risk clinical contexts. Importantly, the results emphasize that acid-suppressive therapy should be guided by individualized risk assessment rather than routine or indiscriminate use. Although safety concerns related to long-term proton pump inhibitor therapy warrant careful consideration, the evidence supports their targeted and time-limited use when the risk of gastrointestinal bleeding is substantial. The observed heterogeneity across included studies reflects real-world variation in patient populations and clinical practices but does not undermine the consistency of findings favoring proton pump inhibitors. Overall, this meta-analysis reinforces current evidence-based recommendations advocating for the preferential use of proton pump inhibitors in patients at moderate to high risk of gastrointestinal bleeding while underscoring the importance of ongoing evaluation, deprescribing strategies, and adherence to risk-based protocols. Future research should focus on optimizing treatment duration, refining patient selection, and balancing efficacy with safety to further enhance gastrointestinal bleeding prevention strategies in clinical practice.

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