

REVIEW ARTICLE

Beyond Mechanical Hemostasis: An Integrative Review on the Efficacy of Combined Endoscopic Therapy and Acid Suppression in High-Risk Peptic Ulcer

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SUMMARY

Introduction: Peptic ulcer bleeding maintains a stable mortality rate despite therapeutic advances. Failure of initial hemostasis and rebleeding in high-risk lesions (Forrest Ia-IIa) drive the search for strategies that surpass monotherapy. The objective of this review was to evaluate the comparative efficacy of endoscopic therapy combined with acid suppression versus monotherapy, analyzing the impact of new pharmacological agents.

Methods: An integrative review was conducted following the framework of Whittmore and Knafelz (2005). The PubMed, Scopus, Web of Science, and Cochrane databases (2015–2025) were searched using MeSH and free text terms. Clinical trials, meta-analyses, and cohort studies comparing dual therapy (mechanical/thermal + pharmacological) versus monotherapy in adults with high-risk ulcers were included.

Results: The synthesis of evidence confirms the superiority of combination therapy over monotherapy in reducing rebleeding and the need for rescue surgery. Epinephrine injection as a single treatment is considered obsolete due to its high failure rates (10–30%). High-dose proton pump inhibitor (PPI) regimens (80 mg bolus + infusion) are critical for maintaining a pH > 6.0 and stabilizing the clot. Furthermore, the competitive potassium blocker vonoprazan demonstrates non-inferiority and potential pharmacokinetic advantages over PPIs in rapid metabolizers.

Conclusions: Combination therapy is the indispensable gold standard, orchestrating mechanical hemostasis with biological clot stabilization. Epinephrine monotherapy is discouraged, and a shift toward precision pharmacology with competitive potassium blockers is emerging.

Keywords: Peptic Ulcer, Gastrointestinal Bleeding, Endoscopic Hemostasis, Proton Pump Inhibitors, Vonoprazan, Rebleeding, Combination Therapy.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) secondary to peptic ulcer continues to be one of the most prevalent and challenging gastroenterological emergencies worldwide, with a mortality rate that, despite therapeutic advances, remains stable at around 5–10% (1,2). Although digestive endoscopy has become established as the cornerstone for diagnosis and initial hemostasis, rebleeding occurs in 10–20% of patients, particularly those with high-risk stigmata, such as Forrest Ia (spurting), Ib (oozing), and IIa (visible vessel) ulcers (3,4). This therapeutic failure not only increases the need for salvage surgery, but also directly impacts hospital stay and healthcare costs (5,6).

The pathophysiology of rebleeding is closely linked to gastric acidity. A low pH environment promotes fibrin clot lysis and impairs platelet aggregation, preventing lasting hemostasis (7). Under this premise, “combination therapy”—defined as endoscopic intervention (mechanical, thermal, or injection) followed by potent acid suppression—has emerged as the proposed standard of care to mitigate these risks. Several meta-analyses have suggested that monotherapy (endoscopy alone or pharmacotherapy alone) is insufficient for high-risk patients, and that the addition of high-dose proton pump inhibitors (PPIs) is essential to stabilize the clot (4,8). In fact, recent studies confirm that high doses of PPIs are superior to standard doses in reducing rebleeding rates and surgical intervention (9,10).

However, significant clinical controversies persist, justifying a current integrative review. First, the comparative efficacy of different dual hemostasis methods (e.g., clips plus injection versus thermocoagulation plus injection) remains a matter of debate. Second, the emergence of new acid-suppressing agents, such as the competitive potassium blocker (P-CAB) vonoprazan, raises the question whether traditional PPIs remain the best adjunctive option, given emerging evidence of their potential non-inferiority or superiority in mucosal healing (11,12). Finally, the management of

vulnerable populations, such as the elderly with multiple comorbidities or users of antithrombotic drugs, requires a differentiated evaluation of the efficacy of these combined protocols, comparing intravenous versus oral routes of administration in high-risk scenarios (13).

Therefore, the objective of this integrative review is to evaluate the comparative efficacy of endoscopic therapy combined with acid suppression versus monotherapy in preventing peptic ulcer rebleeding. Also, it will analyze the impact of new pharmacological therapies and the implications for high-risk subgroups.

METHODS

Studio design

The present study was developed under the integrative literature review design, rigorously adopting the methodological framework proposed by Whitemore and Knafl (14). This approach was strategically selected for its inherent versatility in allowing the inclusion and synthesis of research with diverse methodologies (both experimental and non-experimental), thus facilitating a holistic and in-depth understanding of the phenomenon of combined hemostasis in real-world clinical practice. The research process was systematically structured in five sequential stages: problem identification, literature search, data evaluation, data analysis, and results presentation.

Search strategy

A comprehensive and systematic literature search was conducted in high-impact and relevant biomedical electronic databases: PubMed (MEDLINE), Scopus, Web of Science, and the Cochrane Library. The search period was deliberately limited to studies published between January 2015 and December 2025 to capture the most recent and relevant evidence on new endoscopic technologies and emerging pharmacological therapies (e.g., vonoprazan).

To accurately query the databases, search algorithms were designed using combinations of MeSH (Medical Subject Headings) terms and free-text keywords, employing the Boolean operators “AND” and “OR”. The primary strategy included keywords such as “Peptic Ulcer Hemorrhage,” “Endoscopic Hemostasis,” “Proton Pump Inhibitors,” “Combined Therapy,” “Recurrent Bleeding,” and “High-dose PPI.” Strict language filters were applied to include only scientific literature published in English, Spanish, and Portuguese.

Eligibility criteria

The selection of studies was governed by predefined inclusion and exclusion criteria to minimize selection bias and ensure clinical relevance:

- **Inclusion criteria:** 1) randomized controlled trials (RCTs), meta-analyses, systematic reviews and cohort studies (prospective or retrospective) of high methodological quality; 2) adult population (>18 years) with endoscopically confirmed diagnosis of high-risk bleeding peptic ulcer (Forrest classification Ia, Ib, IIa, IIb); 3) intervention consisting of combined endoscopic therapy (mechanical, thermal, or injection) adjuvanted by pharmacological therapy (PPI or P-CAB); 4) direct comparison versus monotherapy or versus other standard combination regimens; 5) clear reporting of primary clinical outcomes (rebleeding rate, mortality, need for rescue surgery).
- **Exclusion criteria:** Studies conducted in animal models or in vitro, isolated case reports, series with insufficient sample size (<10 patients), grey literature (unpublished theses, conference proceedings without complete peer review), and studies focused exclusively on varicose hemorrhage, given its distinct pathophysiology.

Evaluation of methodological quality

To ensure the reliability and robustness of the synthesized results, the methodological quality of the included studies was assessed using internationally standardized and validated tools, tailored to each study's design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB 2) tool was used, analyzing critical domains such as the randomization process, deviations from planned interventions, and missing outcome data. The quality of observational cohort studies was assessed using the Newcastle-Ottawa Scale (NOS), weighting group

selection, cohort comparability, and objective outcome assessment. This critical appraisal allowed for the weighting of the evidence provided by each study in the final synthesis.

Data evaluation and synthesis

The extracted data were meticulously organized into an evidence matrix that included author/year, study design, sample size, specific intervention protocol, and main findings. Following Whittmore and Knaff's data analysis phase, the information underwent a process of data reduction, visualization, and constant comparison, allowing for the identification of cross-cutting patterns and emerging themes. The synthesis was not limited to a linear chronological description but rather involved thematic grouping into logical and integrative categories: 1) comparative efficacy of endoscopic modalities; 2) acid suppression protocols (PPIs vs. PCABs); and 3) outcomes in high-risk populations.

Ethical considerations

Since this study is an integrative review of publicly available secondary sources, it did not require formal approval from an institutional ethics committee. However, the highest standards of academic integrity and transparency were maintained in the citation and referencing of all primary sources consulted.

RESULTS

A comprehensive literature search and subsequent screening using inclusion criteria allowed for the synthesis of a heterogeneous but convergent body of evidence, providing a comprehensive overview of the current management of gastrointestinal bleeding. The extracted findings were categorized and developed into four fundamental analytical domains.

Critical appraisal of the selected evidence revealed an overall methodological quality of moderate to high. Applying the Cochrane Risk of Bias (RoB 2) tool to the included randomized controlled trials (RCTs) showed that most demonstrated a low risk of bias in the domains of random sequence generation and incomplete outcome data. However, a recurring “uncertain” risk was identified in the domain of participant and staff blinding, a limitation inherent to the interventional nature of endoscopic procedures where operator blinding is technically unfeasible.

Observational and cohort studies assessed using the Newcastle-Ottawa (NOS) scale achieved mean scores above 7 stars, indicating adequate cohort selection and comparability of groups, although some heterogeneity was observed in long-term follow-up. Recent meta-analyses were considered high-quality due to their use of rigorous quantitative synthesis methodologies. Overall, the body of evidence was deemed sufficiently robust to support the clinical conclusions presented below.

Combined endoscopic therapy versus monotherapy

Detailed analysis of the evidence confirms that endoscopic monotherapy (especially epinephrine injection used alone) is a suboptimal strategy and should be considered insufficient for the management of high-risk ulcers (Forrest classification Ia, Ib, IIa). Data were extracted from systematic reviews and international clinical practice guidelines (1,15). They indicate that monotherapy is associated with rebleeding rates that range alarmingly between 10% and 30%. These figures, unacceptable by current quality standards, are attributed to the merely transient effect of epinephrine-induced vasoconstriction, which does not ensure definitive hemostasis once the drug dissipates.

In contrast, combination therapy (endoscopic intervention plus adjuvant pharmacological treatment with a PPI) demonstrates robust statistical superiority, resulting in tangible clinical benefits. Classic studies and their most recent updates (3,4) indicate that adding endoscopic therapy to pharmacological treatment drastically reduces the relative risk of rebleeding compared to pharmacotherapy alone. More critically, dual endoscopic therapy (epinephrine injection followed immediately by a thermal or mechanical method) combined with a proton pump inhibitor (PPI) has been shown to outperform epinephrine injection alone plus a PPI. This multimodal strategy significantly reduces the rate of recurrent rebleeding and the need for emergency surgery by addressing the problem from two angles: initial vasoconstriction to improve visualization and definitive physical hemostasis. However, it is important to note a recurring nuance in the literature: while the reduction in rebleeding and surgery is consistent and reproducible across studies, the reduction in overall all-cause mortality shows considerable variability. This suggests that mortality in these patients often depends on the decompensation of serious

underlying comorbidities (cardiovascular, renal) rather than on the failure of the endoscopic intervention per se.

Dose, timing and stability of the clot

The effectiveness of mechanical or thermal hemostasis depends intrinsically on the stability of the fibrin clot, which is a highly pH-dependent process; pepsin activated in an acidic environment dissolves clots, and platelet function is severely compromised at low pH. The meta-analyses by Zhu et al. (9,10) provide high-quality evidence comparing various PPI administration regimens to determine the optimal pharmacodynamic profile. The findings unequivocally indicate that the high-dose regimen (standardized as an 80 mg intravenous bolus followed by a continuous infusion of 8 mg/h for 72 hours) is superior to standard-dose or intermittent regimens in preventing post-endoscopic rebleeding, specifically in ulcers with high-risk stigmata.

These studies quantify a significant reduction in the rate of endoscopic reintervention and in hospital stay in the high-dose group, attributing this success to the ability to maintain intragastric pH above 6.0 in a sustained manner. Regarding the route of administration, Zhang et al. (13) demonstrated that, although high-dose oral therapy can effectively raise gastric pH, intravenous administration is imperative in the acute-hyperacute phase (first 24–72 hours). The IV route ensures the immediate and sustained bioavailability necessary to neutralize the acidic environment at the critical time of clot formation, whereas the oral route can be affected by impaired gastric perfusion or intolerance in unstable patients.

Clips versus heat therapy

Evidence suggests that the choice of the “second method” in dual therapy (after the initial epinephrine injection) should not be random but rather based on the morphological characteristics of the lesion. Although there are no statistically significant differences in overall mortality when comparing hemostatic clips versus thermocoagulation (bipolar or heat probes), detailed subgroup analyses (3) favor the use of hemoclips in specific anatomical situations. Particularly in large ulcers (>2 cm), with hardened fibrotic bases or visible large-caliber vessels (>2 mm), thermocoagulation may be insufficient due to the “heat dissipation” effect of blood flow or risky due to the depth of the lesion. In these scenarios, the clip offers direct mechanical

compression that does not depend on the tissue response to heat, reducing early rebleeding rates. Therefore, epinephrine injection as monotherapy is definitively relegated to a merely adjunctive role to clarify the visual field before applying definitive therapy.

Competitive potassium blockers (P-CABs)

A persistent gap in conventional PPI therapy is the interindividual variability in therapeutic response, primarily due to genetic polymorphism of the cytochrome CYP2C19 gene. This review identifies vonoprazan as a pharmacokinetically superior alternative that could overcome these limitations. Unlike traditional PPIs, which require an acidic environment for activation and bind irreversibly, vonoprazan competitively and reversibly inhibits the proton pump, does not require acid activation, and has a longer plasma half-life.

Recent high-impact studies (11,12) report non-inferiority rates in preventing rebleeding when comparing vonoprazan with potent PPIs (esomeprazole or lansoprazole). The most relevant and disruptive finding is its sustained efficacy in patients identified as CYP2C19 rapid metabolizers, a subgroup that traditionally experiences higher rates of treatment failure with standard PPIs due to rapid drug degradation. Furthermore, visibly faster mucosal healing rates are documented in second-look endoscopic assessments at 2 and 4 weeks, suggesting significant potential for shortening maintenance treatments and reducing the costs associated with prolonged therapies.

DISCUSSION

This integrative review synthesizes and critically analyzes the most current evidence, from 2015 to 2025, to address one of the most persistent and challenging questions in emergency gastroenterology: how to optimize hemostasis in high-risk peptic ulcers to definitively break the vicious cycle of rebleeding, prolonged hospitalization, and mortality? The findings confirm a profound therapeutic paradigm shift: the specialty has moved from a purely “mechanical” and technical approach to a strategy of “comprehensive biological hemostasis.” In this new model, the synergy between dual endoscopic therapy and aggressive acid suppression is not just another therapeutic option, but a clinical imperative to ensure patient survival.

The superiority of combination therapy over monotherapy, consistently and robustly demonstrated in our results, finds its deep molecular justification in the biology of coagulation. Endoscopic hemostasis, whether through the application of mechanical clips or thermocoagulation, provides immediate physical containment, acting as a mechanical “vascular plug.” However, it is crucial to understand that this plug is extremely vulnerable and unstable in the hostile environment of the stomach.

The primary fibrin clot is susceptible to rapid degradation by acid-induced fibrinolysis and proteolytic activation by pepsin. This is consistent with the classic pathophysiological postulates of Laine and McQuaid (7) and reaffirmed by contemporary meta-analyses by Zhu et al. (10). It has been established that platelet function and the structural integrity of the fibrin clot are practically nil when gastric pH drops below 6.0. In an acidic environment (pH < 4.0), platelets lose their ability to aggregate and the clots formed dissolve (lysis) within minutes due to peptic digestion.

Therefore, “combination therapy” should not be understood simply as the arithmetic sum of two independent interventions, but rather as the orchestration of two complementary and interdependent pathophysiological mechanisms: endoscopy stops active bleeding (“physical damage control”), while high-dose PPIs create the necessary alkaline environment (“chemical life support”) for that control to be lasting and progress toward stable healing. This mechanistic understanding categorically disqualifies the use of monotherapy in Forrest Ia, Ib, and IIa ulcers; relying exclusively on a metal clip without aggressively neutralizing gastric acidity invites therapeutic failure due to secondary clot lysis and late rebleeding.

A critical and defining finding for contemporary clinical practice is the definitive obsolescence of epinephrine injection as a sole treatment. Historically used for its availability and low cost, current evidence is overwhelmingly against it. Although its potent vasoconstrictive effect facilitates immediate visualization of the field by reducing local blood flow, its tissue half-life is dangerously short (from minutes to a few hours). Once the pharmacological effect dissipates, rebound vasodilation occurs, which, combined with the lack of a permanent mechanical seal, explains the unacceptable rebleeding rates (10–30%) reported in both classic and modern literature (1).

Current evidence indicates that the use of epinephrine without secondary therapy (thermal or mechanical) borders on malpractice in the management of high-risk ulcers. Its role should be redefined and relegated exclusively to a bridging or preparatory adjunctive therapy function, intended to clear the field of vision to allow for the precise application of definitive therapy.

Regarding the technical dichotomy of clip versus coagulation, although the overall reported mortality is statistically similar between both modalities, the disaggregated data from studies such as those by Chiu et al. (3) suggest a significant tactical advantage of hemoclips in specific anatomical scenarios. In large ulcers (>2 cm) or those with fibrotic and hard bases, thermal coaptation (bipolar or heater probe) is often ineffective. This is because fibrous tissue conducts heat poorly, and the blood flow from large vessels (>2 mm) produces a heat-sink effect that prevents vessel welding. In these complex scenarios, the clip offers superior mechanical closure through direct physical approximation of the edges, independent of the tissue's thermal response. This implies that the choice of method in the endoscopy suite should not be random or based solely on operator preference but rather tailored to the morphology and chronicity of the ulcerous lesion.

This review highlights the emergence of competitive potassium blockers (P-CABs), and specifically vonoprazan, as a potential game changer, which could redefine acid suppression protocols. The most significant historical limitation of conventional PPIs has been their pharmacokinetic variability and their dependence on the CYP2C19 genotype. A considerable proportion of the population (especially in Asia and Latin America) are rapid or ultrarapid metabolizers, who degrade the drug before achieving sustained acid inhibition, leaving windows of nocturnal acidity that put clotting at risk.

Previous studies (11,12) suggest that vonoprazan, possessing a reversible competitive binding mechanism and being independent of the CYP2C19 metabolic pathway, ensures a pH > 6.0 more quickly, stably, and predictably from the first dose. This is without the need to reach the steady state required by PPIs (3–5 days). While non-inferiority has been the statistically demonstrated standard to date, it is plausible to hypothesize that, in populations with a high prevalence of rapid metabolizers, vonoprazan could outperform PPIs in real-world clinical efficacy, reducing refractory rebleeding rates. Furthermore,

evidence of faster mucosal healing observed in revision endoscopies indicates additional benefits in terms of long-term cost reduction and shorter hospital stays.

The main strengths of this review lie in its integrative, rigorous, and up-to-date approach. Unlike previous, more limited meta-analyses, we have incorporated emerging evidence on P-CAB and stratified the results by specific endoscopic modalities, offering more granular and practical guidance for clinicians. However, we acknowledge inherent limitations that must be considered. First, there is methodological heterogeneity in high-dose protocols between older and more recent studies, introducing confounding variables. Furthermore, a notable mortality paradox persists: despite the dramatic and statistically significant reduction in rebleeding rates and the need for rescue surgery with combination therapy, a reduction in overall all-cause mortality remains elusive in many clinical trials. This suggests an epidemiological reality of modern medicine: mortality from peptic ulcers today is more closely linked to the systemic decompensation of serious pre-existing comorbidities (cardiovascular events, renal failure, aspiration pneumonia) in elderly and frail patients than to direct exsanguination from the ulcer. Therefore, endoscopic success is a necessary, but not sufficient, condition for the survival of the complex geriatric patient.

In conclusion, the clinical management of gastrointestinal bleeding from peptic ulcers has evolved radically, transitioning from a piecemeal approach to a precision science grounded in pathophysiological evidence. The synthesis of the data presented incontrovertibly establishes that combined endoscopic therapy, supported by aggressive and continuous acid suppression, constitutes the indispensable gold standard for high-risk patients, relegating monotherapy to the archives of obsolete practices. While a therapeutic hierarchy is being clarified in which epinephrine injection is merely an adjunct, the choice between clips or thermocoagulation must be dynamically personalized according to the anatomy of the lesion. The immediate horizon points toward precision pharmacology with the consolidation of vonoprazan. Ultimately, therapeutic success does not lie in a single intervention but in the meticulous orchestration of immediate mechanical hemostasis, biological stabilization of the clot, and comprehensive management of the patient's comorbidities.

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Conflicts of interest

The authors declare no commercial conflicts of interest.

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