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Contemporary Approaches to Treating and Preventing Acid-Dependent Digestive Tract Disorders in Patients with Ischemic Heart Disease

Raupov Abdurahmon Ortiq o'g'li
Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi.,
raupov.abdurahmon@bsmi.uz

Resume: This article emphasizes the problems of comorbidity between ischemic heart disease and acid-dependent gastrointestinal disorders in patients. The role of inflammation, metabolic imbalance, pharmaceutical interactions, common risk factors, and pathophysiological relationships are examined. It is proven that contemporary therapy and prevention strategies, such as the use of proton pump inhibitors, cytoprotectors, and Helicobacter pylori elimination, are beneficial. In order to maximize the clinical management of patients with comorbid diseases, the article offers suggestions.

Keywords: cytoprotectors , helicobacter pylori , proton pump inhibitors , pantoprazole.

Gastrointestinal complications are relatively common among individuals with cardiovascular diseases. According to A.L. Vertkin et al., postmortem examinations revealed erosive and ulcerative lesions of the gastrointestinal tract in 28% of patients who died from ischemic heart disease (IHD), in 23.9% of those who succumbed to myocardial infarction, and in 33.7% of patients with chronic heart failure (CHF). In most cases, these mucosal defects were accompanied by bleeding episodes. Gastrointestinal hemorrhage occurred in 40% of IHD cases, in 44.1% of myocardial infarction cases, and in 35.3% of those with CHF [1].

The authors identified several key risk factors predisposing patients to gastrointestinal bleeding, including advanced age (over 70 years), arterial hypertension (reported in 100% of the cases), and chronic heart failure classified as NYHA functional class III–IV (65%). Moreover, a correlation was established between bleeding risk and a reduced left ventricular ejection fraction ranging between 22% and 60%. Notably, nearly half of the deceased individuals (44.9%) had been taking low doses of acetylsalicylic acid (ASA) [1].

The ulcerogenic properties of ASA have long been recognized. In a comprehensive analysis conducted by J. Iwamoto et al. (2013), erosive lesions were identified in 48.4–63.1% of patients receiving low-dose ASA therapy, ulcers were observed in 7.4–31.7%, and the overall risk of bleeding increased by a factor of 2.6 (95% CI: 2.2–2.9) [2]. Importantly, the development of ASA-induced gastric injury was shown to be independent of dosage. In a controlled clinical experiment, B. Cryer and M. Feldman investigated the effects of ASA on gastrointestinal mucosa in 29 healthy participants who received daily doses of 325 mg (10 subjects), 81 mg (11 subjects), or 10 mg (8 subjects) of ASA for three months. Across all groups, mucosal prostaglandin concentrations declined by approximately 40%, while thromboxane activity decreased by 98%, 90%, and 62%, respectively. Endoscopic assessment revealed erosive or ulcerative lesions in at least one participant per group [3].

No dosage of ASA appears to provide an antiplatelet benefit without exerting a gastrotropic effect. Moreover, the pharmaceutical formulation—whether enteric-coated or plain ASA—does not

significantly alter the incidence of mucosal injury. The relative risk of damage remains at approximately 2.6 for both forms [4]. This effect is directly related to the pharmacodynamic mechanism of ASA. The drug exerts both a local cytotoxic impact on gastric epithelial cells and a systemic inhibition of cyclooxygenase (COX), predominantly COX-1 [2]. COX-1 is constitutively expressed in both platelets and gastric tissues. In platelets, its activation facilitates the conversion of arachidonic acid to thromboxane A_2 (TxA_2), promoting platelet aggregation and vasoconstriction. ASA-induced COX-1 inhibition suppresses TxA_2 synthesis, yielding an antithrombotic effect. In contrast, inhibition of gastric COX-1 reduces the synthesis of protective prostaglandins (PGE_2 and PGI_2), leading to increased gastric acid secretion and diminished mucus production—thus producing a pronounced gastropathic effect [5].

Clinically, aspirin-induced gastropathy is often oligosymptomatic or entirely asymptomatic due to elevated sensory thresholds. Ulcers typically develop in the gastric corpus, whereas erosions are more common in the duodenum, measuring approximately 5–10 mm in diameter. Gastrointestinal bleeding frequently represents the first and sole manifestation of this condition [2]. Risk factors for upper gastrointestinal bleeding in low-dose ASA users include age above 70 years, prior peptic ulcer disease, alcohol consumption, concurrent therapy with glucocorticosteroids or anticoagulants, and *Helicobacter pylori* infection [6]. Eradication of *H. pylori* is a mandatory step in managing NSAID- and ASA-induced gastropathy, as successful eradication significantly lowers ulcer risk. However, infection eradication alone does not fully eliminate ulcerogenic potential in patients who continue antiplatelet or NSAID therapy [7].

Preventive interventions for NSAID-associated gastropathy demonstrate that both *H. pylori* eradication and proton pump inhibitor (PPI) therapy are effective, though PPIs confer superior protection. The risk of developing ulcers or bleeding in patients receiving PPI therapy ranges from 0.9 to 1.6, whereas after eradication therapy it varies from 1.9 to 14.8 [2]. Accordingly, the Maastricht Consensus recommends long-term PPI co-administration in patients treated with NSAIDs, along with eradication therapy where indicated (evidence level 1b, recommendation grade A) [8].

Currently available PPIs include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole—all demonstrating proven efficacy in both preventing and treating aspirin-induced mucosal injury, outperforming H_2-receptor antagonists and placebo [9]. Clinical studies report gastroduodenal lesions in only 1.1–3.7% of patients receiving PPI therapy, compared with 5.4–31.7% in placebo groups [2].

Beyond PPIs and eradication therapy, cytoprotective drugs such as misoprostol and bismuth tripotassium dicitrate have also shown therapeutic benefits. After eight weeks of misoprostol treatment, ulcer healing was achieved in 70% of gastric and 86% of duodenal ulcer cases, compared with 25% and 53% in the placebo group, respectively [10]. Similarly, adding bismuth tripotassium dicitrate to omeprazole therapy accelerated ulcer healing to 68.2% versus 34.8% with omeprazole alone [11].

The question of whether ASA therapy should be discontinued following gastroduodenal complications remains complex. In a clinical trial involving 78 patients receiving ASA and 78 receiving placebo for eight weeks, ulcer recurrence occurred in 10.3% and 5.4%, respectively. Despite this, total mortality and cardiovascular mortality were significantly lower among ASA-treated patients (1.3% vs. 12.9% and 1.3% vs. 10.3%, respectively), suggesting that continuation of ASA may increase bleeding risk but ultimately reduces mortality [2].

Dual antiplatelet therapy—combining low-dose ASA with P2Y12 receptor inhibitors—has been shown to effectively prevent thrombotic events in cardiovascular diseases, though it carries an elevated risk of gastroduodenal bleeding. The relative risk of bleeding is 4.0 for ASA monotherapy, 2.3 for clopidogrel alone, and 7.4 for combined therapy [12]. Therefore, long-term prophylaxis with PPIs becomes essential. However, a 2016 meta-analysis of 12 studies involving 50,277 post-PCI patients reported a modest but significant increase in adverse cardiovascular events with concomitant PPI therapy (overall OR 1.28; 95% CI 1.24–1.32), including myocardial infarction

(OR 1.51) and stroke (OR 1.46) [13]. This is attributed to pharmacokinetic interactions between clopidogrel and PPIs, primarily via the CYP2C19 metabolic pathway. Clopidogrel requires activation through CYP2C19-mediated oxidation to its active metabolite, 2-oxoclopidogrel. Omeprazole, which is also metabolized by CYP2C19, inhibits this enzyme, thereby diminishing clopidogrel efficacy [14].

Since all PPIs undergo hepatic metabolism through the cytochrome P450 system, potential drug–drug interactions are clinically relevant. Pantoprazole and rabeprazole exhibit the weakest affinity for CYP2C19, conferring a lower risk of pharmacokinetic interference [15]. Pantoprazole is primarily metabolized in two steps—oxidation via CYP2C19 and subsequent sulfation by sulfotransferase—resulting in pantoprazole sulfate, a pathway that minimizes cytochrome dependency and potential drug interactions. Moreover, studies assessing the inhibitory constant (Ki) for CYP2C19 in human liver microsomes revealed that pantoprazole has the least inhibitory potency (69.4 ± 9.2 μmol) compared with omeprazole (6.2 ± 0.8 μmol), lansoprazole (0.45 ± 0.07 μmol), esomeprazole (8.6 ± 1.0 μmol), and rabeprazole (21.3 ± 2.8 μmol) [16].

A 2012 clinical study investigating dual antiplatelet therapy combined with PPIs in acute coronary syndrome (ACS) patients (n = 176) found that rehospitalization rates were lowest with pantoprazole (6.66%) compared with omeprazole (48.88%), esomeprazole (17.77%), and lansoprazole (11.11%). Pantoprazole use was associated with the lowest risk of adverse cardiovascular events [17]. Additionally, experimental work by H. Lee et al. demonstrated that pantoprazole exerts anti-inflammatory effects: in rats with indomethacin-induced gastric damage, pantoprazole significantly reduced mucosal TNF-α, IL-1β, and IL-8 concentrations, mitigating injury severity [18].

In a randomized, double-blind trial of 160 patients with ASA-induced gastric or duodenal ulcers or erosions (with or without bleeding), participants continued low-dose ASA (80 mg daily) and were assigned to either famotidine (40 mg twice daily) or pantoprazole (20 mg morning dose plus evening placebo). After 48 weeks, recurrent ulcers or erosions occurred in 20% of the famotidine group but in none of the pantoprazole group. Bleeding was noted in 7.7% versus 0%, and dyspeptic symptoms in 12.3% versus 0%, respectively [19].

Taken together, pantoprazole demonstrates outstanding efficacy in both treatment and prevention of NSAID- and ASA-associated gastrointestinal lesions. Its distinctive advantage lies in its minimal interaction potential due to limited dependence on CYP2C19-mediated metabolism.

Conclusion

A practical management algorithm for patients with high cardiovascular risk and concomitant risk of gastropathy should include:

1. **Baseline risk assessment** – Evaluate patient age (>70 years), history of peptic ulcer or complications, and concomitant use of anticoagulants, corticosteroids, or NSAIDs prior to initiating ASA therapy.
2. **Preventive co-therapy** – In patients with additional risk factors, initiate PPI prophylaxis once daily concurrently with ASA.
3. **Screening for *H. pylori*** – Conduct diagnostic testing for infection.
4. **Eradication therapy** – Perform eradication if infection is confirmed.
5. **Endoscopic monitoring** – Conduct follow-up endoscopy three months after initiating ASA treatment.
6. **Treatment of mucosal injury** – If ulcers or erosions are detected, administer therapeutic-dose PPI twice daily combined with a bismuth compound for eight weeks, followed by long-term maintenance with once-daily PPI prophylaxis.
7. **Dual antiplatelet therapy** – For patients receiving combined ASA and clopidogrel therapy, initiate pantoprazole 40 mg daily and continue indefinitely.

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