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The Problem of Aspirin-Induced Gastrointestinal Tract Lesions in Patients with Stable Ischemic Heart Disease Receiving Acetylsalicylic Acid

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Resume: Erosive and ulcerative lesions of the gastrointestinal (GI) tract are common in patients with cardiovascular diseases, particularly those with ischemic heart disease (IHD). Numerous studies demonstrate that acetylsalicylic acid (ASA), widely used for secondary prevention of cardiovascular events, significantly increases the risk of mucosal injury throughout the GI tract. Gastric and duodenal erosions occur in up to 63% of patients, while ulceration and bleeding may develop in up to 40% and 7.7% of cases, respectively. These complications are strongly associated with patient age, concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, corticosteroids, Helicobacter pylori infection, and arterial hypertension. ASA-related enteropathy, although less studied, manifests in up to 71% of long-term users and may lead to anemia, protein loss, or intestinal obstruction. Importantly, a significant proportion of patients remain asymptomatic until complications such as bleeding arise. Despite the widespread use of gastroprotective therapy, no universal preventive strategy has been established to fully mitigate ASA-induced enteropathy or colopathy. The findings highlight the need for individualized risk assessment and close endoscopic monitoring in patients with IHD receiving long-term ASA therapy.

Keywords: Aspirin, ischemic heart disease, gastrointestinal bleeding, erosive gastritis, ulcer disease, proton pump inhibitors, helicobacter pylori, cardiovascular prevention.

In patients with cardiovascular pathology, erosive and ulcerative lesions of the gastroduodenal zone are quite common. According to some authors, gastric erosions and ulcers were found in 28% of autopsy cases in patients with chronic ischemic heart disease (IHD) [1]. In another study by the same authors, gastrointestinal bleeding occurred in 40% of patients with IHD overall and in 44.1% of those with myocardial infarction. In addition to erosive and ulcerative processes, such patients almost always exhibit inflammatory, hyperplastic, and metaplastic changes of the gastrointestinal mucosa . There are several risk factors that contribute to erosive and ulcerative gastrointestinal (GI) lesions in patients with IHD. These include age over 60, and especially over 75 years [2], a history of gastrointestinal bleeding, concomitant use of NSAIDs, anticoagulants, corticosteroids, and the presence of *Helicobacter pylori* (H. pylori) infection . Arterial hypertension (AH) is another important risk factor for GI tract injury manifested as erosions, ulcers, and bleeding, which is observed in nearly 100% of patients with IHD [3]. In recent years, the combined course of AH and erosive-ulcerative processes of the GI tract has been increasingly studied. Data indicate that they share common etiological factors—hereditary predisposition, stress, smoking, alcohol abuse, and a highly excitable type of nervous activity .

A common cause of erosive and ulcerative GI tract lesions in patients with IHD is long-term administration of acetylsalicylic acid (ASA). Similar to other NSAIDs, ASA can induce various GI tract injuries along almost its entire length—from the esophagus to the rectum—though the upper GI tract is most frequently affected [4]. According to some authors, with prolonged use of low-dose ASA, the incidence of erosive gastritis may reach 22%, while esophageal ulcers occur in up to 0.9%

of cases. The incidence of gastric and/or duodenal erosions can reach 63.1% , and gastric and/or duodenal ulcers up to 40%. The relative risk of gastroduodenal bleeding varies, reaching as high as 7.7% . In the 1990s, results from the large U.S. ARAMIS registry were published, showing that each year about 107,000 patients were hospitalized with GI bleeding or perforations induced by NSAIDs, with a mortality rate of 10–15% [92]. In the SALT study (SALT Collaborative Group, 1991), gastrointestinal bleeding occurred in 1.6% of patients (n = 676) taking 75 mg of aspirin daily, compared to 0.6% in the placebo group (n = 684) . In the FAMOUS study, among 404 patients after three months of regular low-dose ASA use, gastric ulcers were found by endoscopy in 15%, duodenal ulcers in 8.5%, and erosive gastritis in 19% [5].

Another large meta-analysis of 24 randomized controlled trials involving 66,000 participants showed that gastrointestinal hemorrhagic events occurred in 2.47% of cardiac patients receiving ASA versus 1.42% receiving placebo, with a relative risk (RR) of 1.68 (95% CI 1.51–1.88) [6]. According to the ARRIVE study, which included 12,546 patients receiving cardioprotective doses of ASA, gastrointestinal bleeding was reported in 0.97% of cases versus 0.46% in the placebo group (p = 0.0007) . The actual risk of gastrointestinal bleeding and other lesions in real clinical practice may be higher than in randomized trials, which often exclude complex patients . The frequency of such adverse effects is dose-dependent. According to some studies, the incidence of major bleeding among patients taking low-dose ASA (30–81 mg/day) was less than 1%, moderate doses (100–200 mg/day) – 1.56%, and high doses (283–1300 mg/day) – 5%. In a case-control study by J. Weil et al., the risk of GI bleeding decreased with lower ASA doses and was 3.9 (95% CI 2.5–6.3) for 150 mg and 2.3 (95% CI 1.2–4.4) for 75 mg per day [7].

Other studies suggest that there is no ASA dose that achieves an antiplatelet effect without gastrotoxicity. Cryer and M. Feldman analyzed the effects of various ASA doses on the gastrointestinal mucosa. For three months, ten healthy volunteers received 325 mg of ASA daily, while eleven and eight subjects received 81 mg and 10 mg, respectively. In all groups, a 40% decrease in protective prostaglandins of the GI mucosa was observed, and one patient in each group developed erosive-ulcerative lesions of the stomach and/or duodenum [8]. Thus, even minimal ASA doses were found to double the risk of erosions and ulcers. Furthermore, 30–40% of patients taking ASA in doses of 75–100 mg per day exhibited gastric mucosal erosions . Low-dose acetylsalicylic acid (ASA) is comparable to, and may even exceed, the ulcerogenic potential of nonselective NSAIDs. According to a retrospective analysis in which 1,103 patients received ASA therapy and 1,856 patients were treated with other NSAIDs, the incidence of gastrointestinal (GI) lesions was 2.54% and 0.27%, respectively. The higher frequency of GI lesions associated with ASA therapy is possibly related to a more pronounced inhibition of prostaglandin E_2 synthesis [9].

The risk of erosive and ulcerative GI damage during ASA therapy is highest at the beginning of antiplatelet treatment. In a study involving 991 patients with ischemic heart disease (IHD), the risk of ulcer bleeding during ASA therapy was evaluated, and it was found that 45% of complications occurred within the first month of treatment [10]. The clinical presentation of ASA-induced gastroenteropathy is characterized by various forms of dyspepsia and may include worsening of gastroesophageal reflux disease (GERD) . According to a meta-analysis of 31 randomized placebo-controlled studies, dyspeptic symptoms (heartburn, nausea, vomiting, epigastric pain) developed in 5.2–40% of cases, leading to treatment discontinuation in 5–10% of patients . In a large five-year prospective study conducted in Denmark in the 1990s, the rate of hospitalization due to gastrointestinal bleeding during low-dose ASA use was 0.23% [11]. Other researchers have reported that gastropathies (gastric discomfort, GERD exacerbation, peptic ulcers) developed in 30% of patients on long-term ASA therapy. Gastric ulcers (either symptomatic or asymptomatic, including those complicated by perforation or bleeding) occurred in 3% of patients .

A characteristic feature of ASA-induced gastroduodenopathies is often the absence of clinical symptoms [12]. There is a marked imbalance between symptoms and endoscopic findings: approximately 40% of patients with erosive and ulcerative GI lesions report no complaints, while 50% of those with dyspepsia have a normal mucosa. It has been observed that patients with any GI

symptoms are more likely to develop severe complications . Some researchers attribute the absence of symptoms to the formation of higher sensory thresholds associated with the underlying disease. Often, the first and only manifestation of erosive and ulcerative GI lesions is bleeding. Unlike ASA-induced upper GI injury, aspirin-induced pathology of the distal intestine remains poorly studied . Most available data come from studies in which ASA was not analyzed separately from other NSAIDs. According to some authors, small intestinal mucosal damage occurs in up to 71% of patients receiving NSAIDs . In an observational study conducted in Spain, the mortality rate associated with bleeding from the upper and lower GI tract was nearly identical—5.3% and 5.7%, respectively [13].

In a study by E. Smecuol et al., healthy volunteers received 100 mg of ASA daily. After two weeks, capsule endoscopy revealed small intestinal mucosal injury in 50% of participants: petechiae in 60%, erosions in 30%, and ulcers in 10%. The level of fecal calprotectin—a biomarker correlating with histological and endoscopic inflammation—rose fourfold, and the lactulose/mannitol ratio, an indicator of intestinal permeability and barrier function, increased 1.7-fold [14]. Similarly, H. Endo et al. used capsule endoscopy to examine the GI tract in patients taking ASA for more than three months due to bleeding or abdominal pain syndromes; erosions of the small intestine were detected in 63.6% of cases [15]. Thus, small intestinal injury associated with ASA intake is quite common.

NSAID enteropathy is characterized by increased intestinal wall permeability, protein exudation, erythrocyte diapedesis, impaired digestion and absorption, and the development of erosions, ulcers, bleeding, perforations, circular strictures, and, consequently, intestinal obstruction . The main clinical manifestations of NSAID enteropathy include iron deficiency anemia, dyspepsia unresponsive to proton pump inhibitor (PPI) therapy, hypoproteinemia, and hypoalbuminemia. Small intestinal lesions may initially present with massive intestinal bleeding, perforation, or intestinal obstruction. Lesions of the small intestine are extremely difficult to diagnose. R. Casado Arroyo et al. reported an increased risk of lower gastrointestinal bleeding in patients receiving cardioprotective doses of ASA [16]. ASA-induced colonic lesions may present as acute colitis, solitary ulcers, or exacerbation of chronic inflammatory bowel diseases [17]. To date, there are no established preventive strategies for ASA-induced enteropathy or colopathy. Moreover, it remains unclear whether the incidence of these lesions increases with the use of enteric-coated ASA formulations.

Conclusion. Aspirin-induced gastrointestinal injury remains a significant clinical problem among patients with stable ischemic heart disease. Even low doses of acetylsalicylic acid can double the risk of erosive and ulcerative lesions, with many patients developing complications in the absence of clinical symptoms. The incidence of GI bleeding increases with higher ASA doses and concomitant use of other ulcerogenic medications. Small intestinal and colonic injuries associated with ASA are increasingly recognized but remain underdiagnosed due to their nonspecific presentation. Preventive strategies, including the use of proton pump inhibitors and eradication of *H. pylori*, may reduce but not eliminate the risk. Therefore, early identification of high-risk patients, careful dose selection, and regular endoscopic assessment are essential components of modern cardiogastroprotective management in patients receiving long-term antiplatelet therapy.

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