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Low-Dose Aspirin-Induced Upper Gastrointestinal Injury-Epidemiology, Management and Prevention

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Low-dose aspirin, defined as 75-325 mg daily, is widely used for the primary and secondary prevention of cardiovascular (CV) events. Currently, approximately 36% of the adult US population more than 50 million people are estimated to take aspirin regularly for CV protection [1]. The low-dose aspirin use may induce a wide range of adverse side effects in the upper gastrointestinal (GI) tract, which range from troublesome symptoms to life-threatening peptic ulcer bleeding, perforation [2] and even death [3].

Both upper GI symptoms and gastroduodenal erosions are very common in low-dose aspirin users. The point prevalence rates of upper GI symptoms and gastroduodenal erosions in low-dose aspirin users are approximately 31% and 60%, respectively [4,5]. Most of low-dose aspirin-related peptic ulcers are asymptomatic. A multi-nation trial revealed that only 20% of low-dose aspirin related peptic ulcers were associated with dyspeptic symptoms [4]. A prospective study demonstrated that the 12-week cumulative incidence of endoscopic ulcers in low-dose aspirin users was 7% [6]. The annual incidence of major GI bleeding in patients receiving low-dose aspirin therapy ranges from 0.07% to 1.57% [7-10].

Low-dose aspirin users who develop an acute peptic ulcer bleeding event represent a serious challenge for physicians. Withdrawal of low-dose aspirin in the subjects taking low-dose aspirin for CV protection is associated with a threefold increase in the CV event risk [11]. A randomized, placebo-controlled trial [12] also disclosed that bleeding ulcer patients who stopped taking aspirin treatment after endoscopic hemostasis therapy had a higher 56-day all-cause mortality rate than those who kept taking aspirin (12.9 vs 1.3%). However, the former had an insignificantly lower rebleeding rate than the latter (5.4% vs 10.3%). The physicians therefore should balance the risks of CV events and rebleeding in the management of low-dose aspirin-related peptic ulcer bleeding. In general, stopping antiplatelet therapy during acute ulcer bleeding in patients taking low-dose aspirin for primary prevention of CV events is reasonable. In contrast, early resumption of antiplatelet agent with a proton pump inhibitor (PPI) in bleeding ulcer patients who take aspirin for secondary CV protection is strongly recommended [12].

It is still unclear when is the best timing for re-starting low-dose aspirin therapy in low-dose aspirin users with acute ulcer bleeding. Several prospective studies showed that most of the rebleeding events in patients with peptic ulcer bleeding occurred in the first 3 days of admission [13]. Theoretically, aspirin can permanently inactivate the COX activity of platelets, and the antiplatelet effects of aspirin may last for a few days after cessation of aspirin. A prospective study by Komatsu et al. documented that the bleeding time returned to normal values at 3 days following discontinuation of aspirin in healthy subjects [14]. A cohort study [15] showed that most events of strokes related to discontinuation of antiplatelet agents occurred between 6 and 10 days following cessation of antiplatelet agents. Therefore, resuming antiplatelet agents at 3-5 days after the last dosing of aspirin is a reasonable strategy in the treatment of bleeding ulcer patients who take aspirin for secondary prevention of CV diseases and have high-risk bleeding stigmata at initial endoscopy [16]. Nonetheless, bleeding ulcer patients with clean-base ulcers at initial endoscopy can continue antiplatelet therapy immediately following endoscopic assessment.

In the management of uncomplicated peptic ulcers for low-dose aspirin users, the physicians should also balance the risks of GI injury and benefits of CV protection of antiplatelet therapy. Early resuming antiplatelet agents is indicated for patients with previous CV events. Besides those taking aspirin for secondary CV protection, the American Heart Association also recommends prophylactic aspirin to the subjects with a 10-year CV risk 10% [17]. The 10-year CV risk of an individual subject can be assessed by the Framingham calculator (website: http://hin.nhlbi.nih.gov/atpii/calcualtor.asp?usertype=prof). A recent study by Liu et al. demonstrated that there were no differences in the ulcer healing rates between ulcer patients receiving PPI-plus-aspirin and PPI alone therapies [18]. Therefore, prescribing a powerful PPI with continuation of aspirin is recommended in the treatment of uncomplicated peptic ulcer for patients who require low-dose aspirin therapy.

For the long-term prevention of recurrent ulcers, patients with a history of complicated or non-complicated peptic ulcer history who require low-dose aspirin therapy for CV protection should be tested for the presence of *H pylori* infection [19]. Eradication therapy is indicated for those with *H pylori* infection. Additionally, patients should also be assessed for other risk factors for peptic ulcers and GI bleeding such as concomitant use of NSAID or anticoagulant. Co-therapy with an antisecretory agent, preferably a PPI, is recommended for those with a high risk for ulcer complications [20]. Several randomized, control trials [20] demonstrated that co-therapy with PPI significantly reduced the rate of recurrent bleeding in low-dose aspirin users with prior histories of bleeding ulcers. Though H_2 receptor antagonist can reduce the risk of upper GI bleeding in low-dose aspirin users, it is inferior to PPI in preventing recurrence of aspirin-related peptic ulcers or erosions [21].

.In conclusion, low-dose aspirin therapy is associated with upper GI side effects ranging from dyspepsia, gastroduodenal erosions, and asymptomatic endoscopic ulcers to complicated peptic ulcers. Early resumption of antiplatelet agent with co-therapy of a PPI is strongly

recommended in the management of bleeding ulcer patients who take aspirin for secondary CV protection and have high-risk bleeding stigmata at initial endoscopy. The optimal timing to restart antiplatelet agents in bleeding ulcer patients who undergo antiplatelet therapy remains unclear but resuming low-dose aspirin at 3-5 days after the last dosing is a reasonable strategy. In the treatment of low-dose aspirin-related uncomplicated of peptic ulcers, continuing aspirin plus a powerful PPI is recommended for those requiring antiplatelet therapy. For the prevention of recurrent peptic ulcers and ulcer complications, eradication therapy is indicated for *H pylori* infected aspirin users who have an ulcer history. Additionally, co-therapy with a PPI is recommended for those with a high risk of ulcer complications.

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