Long-Term Care Updates

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Oral Anticoagulants and Gastro-intestinal Prophylaxis

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By Cami Bizal, PharmD Candidate

Introduction

Oral anticoagulants, including novel oral anticoagulants (NOACs) and vitamin K antagonists (VKA), are used for various indications such as stroke prevention in patients with atrial fibrillation (AF), venous thromboembolism (VTE), and status post heart valve replacement.[1] NOACs, including direct thrombin inhibitor dabigatran and direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have been increasing in popularity in the prevention of embolic stroke in nonvalvular AF and both treatment and prevention of VTE. All anticoagulants can cause bleeding, which includes gastrointestinal bleeding (GIB). Overt GIB is managed by holding NOACs, followed by delaying endoscopic treatment. In the case of severe bleeding, specific reversal agents can be used along with urgent endoscopic management.[2]

Antisecretory drugs such as proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RA) are effective in treating acid-related disorders and are typically used and tolerated in the short-term, up to 12 weeks. Long-term treatment with PPIs has been associated with rare, but severe adverse effects.[3] PPI therapy is appropriate for patients requiring antiplatelet therapy and with multiple risk factors for GIB.[4]

This newsletter will address the clinical evidence related to gastrointestinal (GI) prophylaxis in patients on oral anticoagulation therapy as well as recommendations for deprescribing antisecretory therapy in patients not indicated for therapy.

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Clinical Evidence

The American College of Cardiology Foundation (ACCF)/ American College of Gastroenterology (ACG)/ American Heart Association (AHA) Expert Consensus discusses reduction of GI risks of antiplatelet therapy, with and without nonsteroidal anti-inflammatory drug (NSAID) use, and recommendations for the use of antisecretory therapy in patients receiving antiplatelet therapy. The use of antisecretory therapy, either a PPI or H2RA, reduces the risk of upper GI bleeding in comparison to no therapy, with PPIs associated with a greater degree of reduction in upper GI bleeding in comparison to H2RAs. PPIs are recommended to generally reduce risk of GI bleeding among patients with a history of upper GI bleeding, who are at the highest risk for recurrent bleeding, especially while on antiplatelet therapy. Patients with advanced age; concurrent use of anticoagulants, steroids, or NSAIDs; or *Helicobacter pylori* infection are also at increased risk of GI bleeding, with an increase of bleeding risk as the number of risk factors increases. PPI therapy is appropriate in patients requiring antiplatelet therapy with multiple risk factors for GI bleeding. Use of antisecretory therapy in patients with lower risk of upper GI bleeding is not recommended as these patients have less potential benefit from prophylactic therapy. It is recommended that clinical decisions regarding concomitant antisecretory therapy in patients on antiplatelet therapy must balance overall risks and benefits, considering both cardiovascular (CV) and GI complications. The guidelines make no recommendations about the use of anticoagulants, except as concomitant therapy with antiplatelet therapy.[4]

The evidence supporting efficacy of antisecretory agents for GI protection in patients on oral anticoagulant therapy has been mixed.

A meta-analysis from Ahn et al. showed that PPI co-therapy in patients receiving oral anticoagulants is associated with lower total and major GIB, except for patients on edoxaban.[5] A systematic review and meta-analysis from Kurlander et al. seconded these results, but acknowledged the evidence was drawn from mostly observational studies with a low risk of bias. They determined the most apparent, considerable benefits in patients with increased risk of upper GIB.[6] A third meta-analysis determined that the use of concomitant PPI therapy with recommended antithrombotic therapy in patients with coronary artery diseases could reduce the risk of gastrointestinal events and significant bleeding from gastroduodenal lesions. However, concomitant PPI therapy may not affect the incidence of major adverse cardiovascular and cerebrovascular events (MACCE), all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and gastroduodenal ulcer.[7] A cohort study in Denmark and the Netherlands also indicated that concomitant treatment with PPI therapy in patients with AF on NOAC is associated with a reduced risk of severe upper GIB. From this study, the researchers recommended the consideration of PPI co-treatment in patients on oral anticoagulant therapy, especially in elderly patients, patients with a HAS-BLED score (hypertension, abnormal liver/ renal function, history of stroke, bleeding tendency, labile INRs, elderly aged ≥ 65 years, drug/alcohol use) ≥3, and/or in patients on concomitant antiplatelet therapy.[8]

However, evidence also exists showing no significant efficacy of antisecretory agents in the role of gastroprotection in patients on oral anticoagulants. A case-control study from Lanas et al. showed no apparent GI protection in patients taking oral anticoagulants when using concomitant PPI therapy, as evaluated by the lack of significant reduction in upper GIB events.[9] A nationwide cohort study in Korea found a lower risk of serious GI complications among elderly patients receiving both NSAIDs and anticoagulants when using a PPI or cyclooxygenase-2 inhibitor as GI preventative strategy, but not complete elimination of risk.[10]

Long-term PPI therapy beyond 12 weeks has been associated with rare, but serious effects such as increased risk of bone fractures, *Clostridium difficile* infection (CDI), increased mortality in older patients, hypomagnesemia, vitamin B12 deficiency, and rebound acid hypersecretion syndrome (RAHS).

In a large placebo-controlled randomized trial, Moayyedi et al. found no association with pantoprazole and any adverse event when used for a duration of 3 years, with the exception of possible increased risk of enteric infections, specifically CDI.[3] Researchers in the United Kingdom conducted two population-based case-control studies and found an increased risk of community-acquired CDI in patients on acid-suppressive therapy, and especially with PPIs.[11] A cohort study from Howell et al. also found the risk of nosocomial CDI to be increased as patient's level of acid suppression was increased.[12] In susceptible populations, case-control studies support an association between prolonged use of PPIs and increased risk of bone fractures.[13] The risk of fracture increases with longer duration of PPI therapy and use in post-menopausal women with a history of smoking, which is known to inhibit calcium absorption.[14] Nutritional deficiencies of vitamin B12, iron, and magnesium are proposed with acid suppressive therapy due to the interference with proteolytic digestion of dietary protein-bound vitamins in the stomach and promotion of bacterial overgrowth in the small intestine.[13] The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom warn providers of the risk of hypomagnesaemia with prolonged use of PPIs greater than one year. Serious manifestations of hypomagnesaemia include fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmias. For patients expected to be on prolonged PPI treatment, healthcare professionals should consider monitoring serum magnesium levels before starting PPI treatment and repeating monitoring periodically during treatment.[15] RAHS results in gastric acid secretion above levels prior to treatment with acid suppression when acid suppression is stopped. Without consistent and compelling data that PPI withdrawal procedures invoke symptomatic rebound, evidence-based guidelines should be followed.[13] Public Health England recommends giving consideration to reviewing the need and/or stopping PPIs in patients with or at high risk of CDI, including recent antibiotic use, hospitalization, advanced age, underlying morbidity, and inflammatory bowel disease.[16] Overall evidence for long-term complications from PPI therapy is limited by the absence of high quality randomized-controlled trial data.[13]

The American Gastroenterological Association (AGA) provides recommendations for de-prescribing PPIs in their most recent Clinical Practice Update from February 2022, and key recommendations are highlighted as follows. All patients taking PPIs should have regular review of the ongoing indications for use and documentation of that indication. All patients without definitive indication for chronic PPI use should be considered for trial of deprescribing. Patients at high risk of upper GIB, as assessed with an evidence-based strategy, should not be considered for PPI deprescribing. Either dose tapering or abrupt discontinuation strategies can be considered when deprescribing PPIs.[17]

A Korean cohort study identified that of patients on an oral anticoagulant with concomitant PPI therapy, NOACs were associated with lower risk of upper GIB and mortality compared to warfarin. There was no difference between the oral anticoagulants in regards to efficacy parameters for stroke prevention. In patients with higher GIB risk, NOACs may be preferred over warfarin for decreasing risk of upper GIB and mortality.[18] Concomitant PPI protective therapy was associated with lower total and major GIB in patients with OAC, except for patients on edoxaban.[5] In comparing the available oral anticoagulants, the National Association of Hospital Cardiologists (ANMCO) determined high-dose dabigatran (150 mg BID), rivaroxaban, and high-dose edoxaban (60 mg daily) to be associated with a higher risk of GI bleeding in comparison to apixaban and warfarin.[19] Patients of older age (>75 years old) and patients receiving dabigatran or rivaroxaban had a greater risk of major GIB. Location of GIB differs in frequency with each OAC, with lower GIB more likely with dabigatran, upper GIB more likely with warfarin and rivaroxaban, and upper and lower GIB occurring at comparable rates with high-dose edoxaban. [2] Additionally, PPIs offer a slightly increased GI protective effect over H2RAs. [20]

Certain comorbidities, past medical history, concomitant medications, and patient characteristics may increase GIB risk and warrant consideration of gastroprotective agents while on oral anticoagulant therapy. Patients of older age, renal impairment, of Chinese ethnicity, with a history of gastroduodenal ulcer, GI bleeding, gastroduodenal perforation, history of ulcer complication or ulcer disease, history of *H. pylori* (treated), HAS-BLED score ≥ 3, colonic diverticulosis, presence of angiodysplasias, and concomitant use of medications known to cause upper GI adverse events (i.e. antiplatelets, SSRIs, NSAIDs) are at increased risk of GIB, with an increase in risk with each additional risk factor.[2,4] Patients should be assessed on an individual basis and reviewed regularly for their individual risks of GIB on oral anticoagulants in comparison with the risks of long-term antisecretory therapy.[2]

Other strategies for prevention of GIB include reviewing the indication for oral anticoagulation, and avoiding anticoagulation in patients with contraindications, and without express indications for treatment. Patients' renal and hepatic function should be assessed and be taken into account when selecting an oral anticoagulant agent. Appropriate dosage should be evaluated for oral anticoagulants in relation to renal and hepatic function. Other renal protective measures, such as avoiding the use of nephrotoxic medications should also be considered on an individual basis. Any modifiable risk factors such as *H. pylori* infection, alcohol use, and concomitant medications that can be discontinued should be addressed.[2]

Conclusion

There are no current clinical guidelines for the use of antisecretory GI prophylactic therapy to prevent GIB in patients on single oral anticoagulant therapy. Guidelines recommend using prophylactic PPI co-therapy in patients on concomitant anticoagulant and antiplatelet therapy with multiple risk factors for GIB or a history of GIB. Patients should be assessed individually based on risk factors for GIB to determine the risks of antisecretory prophylaxis when on an oral anticoagulant in comparison to the risks of GIB.

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