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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: When should antithrombotic therapy be resumed after gastrointestinal bleeding?

A: RESTARTING ANTITHROMBOTIC THERAPY is recommended when indicated in patients after gastrointestinal bleeding, such as those with acute coronary syndromes or atrial fibrillation, or following percutaneous intervention.[1] However, the timing is critical, as premature re-initiation can lead to recurrent bleeding, and delayed re-initiation can increase risk of thromboembolic events.

Antithrombotic therapy decreases unfavorable outcomes secondary to underlying etiology.[1] The timing of re-initiating therapy after gastrointestinal bleeding warrants an individualized approach. The plan may be modified after consideration of factors related to the bleeding event, thromboembolic risk, and patient comorbidities.[1]

MAGNITUDE OF THE PROBLEM

In the United States, antiplatelet and oral anticoagulant (OAC) therapy has increased considerably, from 29.5% in 2011 to 68.0% in 2017 with a sizeable contribution from increased use of novel OACs (non-vitamin K OACs) from 0.1% in 2011 to 43.5% in 2017.[2] Antiplatelet use has also increased, but use of clopidogrel decreased from 100% to 65% by the end of 2011 and leveled off thereafter.[3] In 2013, clopidogrel still remained the most prescribed OAC, and ticagrelor had replaced a substantial portion of prasugrel.[3] Use of the combination of an OAC and single antiplatelet drug (dual therapy) increased from 14.8% in 2011 to 36.3% in 2017, and use of an OAC with dual antiplatelet therapy (triple therapy) increased from 14.6% in 2011 to 31.6% in 2017.[2]

Bleeding commonly complicates antithrombotic therapy. The reported incidence of bleeding associated with OAC therapy varies from 10 to 17 and 2 to 5 per 100 patient years for all bleeding complications and for major bleeding complications, respectively, depending on patient characteristics and underlying diseases[1,4–6] Numerous trials—eg, Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH),[7] Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA),[8] and Secondary Prevention of Small Subcortical Strokes Trial (SPS3)[9] have shown increased risk of early bleeding with dual antiplatelet therapy compared with either separate regimen.[10] Furthermore, triple therapy is associated with higher bleeding risk compared with dual therapy despite similar rates of all-cause mortality.[11]

RISKS AND BENEFITS OF RESTARTING THERAPY

Although resumption of anticoagulant therapy after gastrointestinal bleeding is associated with increased risk of recurrent bleeding, it is also associated with significant decrease in thromboembolic events and all-cause mortality.[12] A number of clinical trials[7,8,13–15] have compared agents for ideal therapy. The WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?)[13,14] reported that dual therapy caused fewer bleeding events than triple therapy, with no excess ischemic events or trade-off in efficacy.

Among OACs, novel OACs were associated with fewer bleeding events compared with vitamin K antagonists (eg, warfarin, acenocoumarol) and were as effective; hence, direct-acting OACs (eg, apixaban, dabigatran, edoxaban, rivaroxaban) are the preferred

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agents.[13] Furthermore, current evidence also favors re-initiating antithrombotic therapy after gastrointestinal bleeding as it leads to better mortality outcomes.[16] Of the P2Y12 receptor inhibitors commonly used (clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor), clopidogrel is preferred as it is effective and has the lowest bleeding risk, followed by ticagrelor.[13]

TOOLS FOR DECISION-MAKING

The HAS-BLED scoring is a useful tool that has been validated for predicting bleeding risk in patients who require OACs, particularly those with atrial fibrillation or flutter.[17] Points are given for hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio (INR), age over 65, use of medications that predispose to bleeding, and consumption of alcohol. A score of 3 or higher indicates a high risk of bleeding (≥ 5.8% per year).[13] Other scoring systems (eg, Glasgow-Blatchford,[18] Rockall[19]) are available and may guide decision-making in specific situations.

TRIVIAL AND MILD BLEEDING

For trivial bleeding, antithrombotic therapy may be continued without interruption.[20–22] For patients with mild bleeding (needing medical attention without hospital stay), dual antiplatelet therapy may be continued, but re-evaluation of the duration of therapy or switching from a stronger (eg, ticagrelor or prasugrel) to a weaker agent (clopidogrel) should be considered.[20–22] For patients on triple therapy, de-escalating to dual therapy may be considered.[13,20] Patients on vitamin K antagonists may be advised to postpone the next dose until the INR is less than 2.[21,23,24] Patients on novel OAC therapy may be asked to skip one dose.[20]

MODERATE BLEEDING

Moderate bleeding is defined by a hemoglobin drop of 3.2 g/dL or bleeding that requires hospitalization in a patient who is otherwise hemodynamically stable.[21,22] For moderate bleeding, interrupting dual antiplatelet therapy and switching to a single agent, preferably a P2Y12 inhibitor (eg, clopidogrel, ticagrelor) is recommended, especially in upper gastrointestinal bleeding.[20,21,25] Dual antiplatelet therapy may be re-initiated within 3 days after gastrointestinal bleeding has stopped, but the duration of therapy may be shortened, and switching from a stronger to a weaker agent should be considered.[20,21,25]

If using OACs, therapy should be discontinued and vitamin K antagonists therapy should be reversed until gastrointestinal bleeding stops, unless very high thromboembolic risk is present: eg, mechanical heart valve, cardiac assist device, or a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke/transient ischemic attack–vascular disease, age 65–74, female sex) score of 4 or higher.[21–23] In patients on dabigatran, activated charcoal may be used if the last dose of novel OAC is within 2 to 4 hours.[21] OAC therapy should be re-initiated within 1 week of gastrointestinal bleeding with a direct-acting OAC at the minimum possible dose, or with a vitamin K antagonist with a target INR of 2 to 2.5.[20,21] If the patient was on triple therapy, de-escalate to dual therapy.[13,20–22]

SEVERE BLEEDING

Severe bleeding is characterized by more than a 4.8-g/dL drop in hemoglobin requiring hospitalization in a patient otherwise hemodynamically stable.[21] In these patients, all recommendations stated for moderate bleeding may apply; however, all antithrombotic medications should be discontinued if bleeding persists despite treatment.[20,21] The need for antiplatelets should be re-evaluated. If needed, the duration of therapy should be shortened and a weaker agent used.[21,22]

If the patient was on OACs, stopping and reversing therapy is indicated unless there is a high risk of thromboembolic events.[21,22] The preferred reversal agent for vitamin K antagonists is a prothrombin complex concentrate.[21,23,26,27] Additionally, the guideline recommends against the use of prothrombin complex concentrates for novel OAC reversal (very low certainty of evidence).[21,26,27] In patients on dabigatran, reversal may be done with idarucizumab, which acts in under 5 minutes.[20–24,28]

Therapy with OACs should be re-initiated, only if indicated, within 1 week of gastrointestinal bleeding, with a direct-acting OAC starting at the minimum dose or a vitamin K antagonist with a target INR of 2 to 2.5.[20–22] If the patient was on triple therapy, de-escalating to dual therapy may be considered.[13,20,21] If the patient is on dual therapy, consider discontinuation if safe.[20,21]

LIFE-THREATENING BLEEDING

In cases of life-threatening bleeding, all antithrombotic therapy should be discontinued immediately.[20,21] If using OAC therapy, discontinue and reverse immediately.[20,21] Re-initiation of antiplatelets in life-threatening bleeding requires additional evaluation with endoscopy and assessment of patient risk factors.[20–22,24]

If a decision is made to restart antiplatelet therapy, a P2Y12 inhibitor should be used, especially in upper gastrointestinal bleeding. If restarting OAC therapy, low-dose apixaban is preferred.[20]

TAKE-HOME MESSAGES

- Use an individualized approach to re-initiate antithrombotic therapy after gastrointestinal bleeding.
- For trivial and mild bleeding, an OAC and antiplatelet drug may be continued with adjustments in the regimen.
- When using antiplatelets for moderate or severe bleeding, periodically re-evaluate the need for these agents. If indicated, re-initiate within 3 days after gastrointestinal bleeding has stopped. However, the duration of therapy may be shortened, and switching from a stronger to weaker agent should be considered. Dual antiplatelet therapy may be switched to a single agent, preferably a P2Y12 inhibitor.
- When using OAC drugs for moderate or severe bleeding, therapy should be re-initiated within 1 week of gastrointestinal bleeding with a direct-acting OAC, starting at the minimum dose, and with vitamin K antagonists with a target INR of 2 to 2.5. If the patient was on triple therapy, de-escalate to dual therapy.
- For life-threatening bleeding, all therapy should be stopped immediately and reversed. After endoscopic evaluation and assessment of patient risk factors, if a decision is made to re-initiate therapy with an OAC, low-dose apixaban is preferred. If restarting antiplatelet therapy, a P2Y12 inhibitor is preferred.

DISCLOSURES

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