

ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Gastrointestinal Endoscopy in Patients Taking Novel Oral Anticoagulants



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G&H How do the novel oral anticoagulants differ from the anticoagulants previously used?

JA In the United States, warfarin was the primary anticoagulant used in the past. Although it is effective at lowering the risk of stroke and systemic blood clots, it is unpredictable in its pharmacokinetics and pharmacodynamics, is affected by dietary vitamin K, and suffers from numerous drug-drug interactions, thus requiring frequent monitoring, which is costly and a nuisance for patients. The novel oral anticoagulants (NOACs)—which currently include rivaroxaban (Xarelto, Janssen), apixaban (Eliquis, Bristol-Myers Squibb), and dabigatran etexilate (Pradaxa, Boehringer Ingelheim)—were designed to eliminate many of these problems. Warfarin works by inhibiting vitamin K-dependent modification of 4 proteins in the clotting cascade, whereas the NOACs act by inhibiting the action of individual proteins in this cascade. Thus, NOACs do not suffer from the numerous interactions associated with warfarin, which allows the novel agents to be administered without regular monitoring or worry about food interactions; in addition, only a few drugs interact with NOACs. Also, dosing is fairly fixed in these agents, so there is no need for individualized dosing, unlike with warfarin. On the other hand, NOACs are more expensive than warfarin, and warfarin does work very well for many people. Nevertheless, large trials have demonstrated that, in comparison with warfarin, the NOACs reduce hemorrhagic stroke by approximately 50%, which is obviously a big benefit.

G&H What is the risk of gastrointestinal bleeding associated with NOACs?

JA Although, in general, NOACs reduce the risk of hemorrhagic stroke and have a comparable risk of major bleeding into all organs compared with warfarin, the large pivotal NOAC trials have demonstrated that the NOACs are associated with a modestly increased risk of gastrointestinal (GI) bleeding compared with warfarin. Warfarin has been shown to increase the risk of major GI bleeding approximately 3-fold over placebo in the atrial fibrillation population, and 3 NOACs have been shown to further increase this risk 1.5-fold compared with warfarin.

G&H How significant is the risk of bleeding during endoscopic procedures performed in patients taking NOACs?

JA This is an area that is ripe for research, as most of the guidance available in the literature on the management of anticoagulants around the time of endoscopic procedures is based on expert opinion and on what makes pathophysiologic sense in the absence of absolute risk data. That being said, anticoagulants increase the risk of bleeding during certain types of endoscopic procedures, and this absolute risk depends on the type of procedure. In its guidelines on the management of anticoagulation around the time of endoscopic procedures, the American Society for Gastrointestinal

Endoscopy has classified endoscopic procedures as low-risk procedures (eg, upper endoscopy and colonoscopy, with or without biopsy) and high-risk procedures (eg, endoscopic sphincterotomy and colonoscopic polypectomy with resection of a large polyp). With warfarin, guidelines have generally recommended that, when possible, anticoagulation be interrupted around the time of higher-risk endoscopic procedures but continued around the time of lower-risk endoscopic procedures. The risks of stopping the anticoagulant (namely, thrombosis and stroke) must be weighed against the risk of hemorrhage; some patients have higher risks of stroke or clot, which affects how safe it is to stop the anticoagulant. In practice, we often end up weighing the relative risks of both options and consult with a cardiologist to make an assessment. So far, there are no practice guidelines from professional societies related to the management of NOACs in this setting.

G&H Does the use of NOACs affect the timing of an elective endoscopic procedure?

JA If the procedure is not urgent and has a low risk of bleeding and the NOAC is continued, it is preferable to perform the procedure when the NOAC is at trough level. For example, if the NOAC is a once-daily drug, the procedure could be performed 20 hours after the patient's last dose to minimize the anticoagulant effect of the drug.

If an elective endoscopic procedure has a high risk of bleeding, it is preferable to stop the NOAC to help promote hemostasis around the time of the procedure. This is when the difference between warfarin and the NOACs is particularly important. The effect of warfarin takes days to attenuate, whereas the half-life of the NOACs is 8 to 12 hours. Thus, if a patient holds his or her NOAC for 24 to 36 hours before an endoscopic sphincterotomy, for example, the patient's coagulation status should be reapproaching normal in the absence of extenuating circumstances, such as renal failure.

There is generally no need to reverse NOACs, nor are good reversal agents for these drugs readily available. The lack of a commercially available antidote often concerns physicians who are not familiar with NOACs because they know that reversal agents are available for warfarin. However, reversal of warfarin is not always rapidly effective, and the liver and kidney metabolize and/or excrete the NOACs rapidly; thus, counterintuitively, there may be more rapid reversal of NOACs without exogenous factors than of warfarin with exogenous reversal agents. It should also be noted that there are a number of agents in the pipeline that are being designed to act as antidotes to NOACs.

G&H If anticoagulation is stopped, what is the optimal timing for restarting NOAC therapy after elective endoscopy?

JA As with warfarin, there is no consensus related to the best time for restarting therapy, nor are there any good data to drive decision-making. Expert guidelines suggest that warfarin be restarted, in most cases, within 24 hours after the endoscopic procedure is completed. A similar type of algorithm would be reasonable for NOACs. To some degree, the optimal timing will be influenced by both the patient's risk of stroke and/or systemic embolus and the risk of postprocedural bleed. Thus, the drug might be held for 48 hours after a high-risk polypectomy in a patient with a modest risk of stroke. It should be remembered that, whereas the anticoagulant effect builds up gradually with warfarin, with NOACs, a patient is fully anticoagulated again 2 to 3 hours after taking the first capsule. This time difference should be taken into account during decision-making.

G&H Is endoscopic evaluation and therapy warranted and safe in patients who are actively bleeding and taking NOACs?

JA It depends on the case. If a patient's bleeding is not rapid, it may be advisable, given the short half-life of the NOACs, to let some time elapse and, in the absence of shock, renal failure, and liver failure, simply support the patient over 12 to 24 hours, thus allowing natural clearance of the drug and normal hemostatic functions to resume. In addition, endoscopic therapy may be easier to perform in a patient who is not fully anticoagulated. Thus, with the NOACs, a few hours may make a big difference, unlike with warfarin.

To determine the safety of endoscopic therapy in patients taking NOACs, we have to consider all of the different factors that would be considered with any anticoagulant. For example, what is the risk of intervening if the patient has a stomach full of blood? Should the patient be intubated? If the patient is very anemic, should he or she be transfused first? Should the patient be placed in an intensive care unit? What other types of resuscitative measures should be considered? Is the patient in renal failure? All of these questions should be taken into consideration to determine the ideal timing of endoscopy in any patient who is on anticoagulants.

G&H Has there been any specific research on the effectiveness of endoscopy in this setting?

JA There is only a little research on this issue. The best data come from the RE-LY trial, which was the large piv-

otal trial on dabigatran etexilate. In that trial, the investigators looked at the data surrounding all of the invasive procedures (including endoscopic procedures) performed in patients on dabigatran etexilate to see whether there was an increased risk for either bleeding or thrombotic complications compared with patients receiving warfarin. Reassuringly, patients receiving dabigatran etexilate did as well as, if not better than, the patients receiving warfarin.

G&H Have any studies examined the effectiveness of clips or other types of mechanical hemostasis in patients on NOACs?

JA We do not have any data on the use of clips in this setting, but because clips are useful in the management of bleeding lesions in the absence of anticoagulation, it certainly makes theoretical sense to use clips in this setting as well. Likewise, it makes sense from a pathophysiologic standpoint to mechanically address the bleeding as well as address it with cautery. One of the problems with cautery is that an eschar can form that can slough after a week to 10 days. In theory, clips may help to mitigate this problem.

G&H When bleeding is controlled via endoscopic hemostasis, what is the optimal timing of restarting NOAC therapy?

JA The answer depends on several factors. First, restarting NOAC therapy depends on the patient's risk of stroke because the lower the risk of stroke, the longer the patient can wait before restarting therapy. Second, the timing of therapy depends on how torrential the bleeding was. The more torrential the bleeding, the longer the patient should wait. Third, restarting therapy depends on the effectiveness of the endoscopic treatment. If the endoscopic therapy was highly effective—for example, only a single lesion was found, which was cauterized and/or clipped, and the endoscopist was sure that the cause of the bleeding was fixed—anticoagulation can be restarted

sooner than if there was uncertainty about whether the active lesion was found and treated. Finally, patients with prior GI bleeding on NOACs are at higher risk for future bleeding on NOACs, so there should be a discussion with the cardiologist to either lower the dose of the NOAC or to switch to warfarin. Additionally, concurrent antiplatelet use raises the rate of NOAC-associated GI bleeding, so, when possible, antiplatelets should be withheld.

G&H What are the next steps in research in this area?

JA From a gastroenterology standpoint, it is important to better understand why NOACs appear to selectively increase the major GI bleeding risk as opposed to the major bleeding risk from other organ systems. There must be a reason for the predilection for bleeding from the GI tract, whether it is because there are concentrations of active anticoagulants in the GI tract or whether it is because of other reasons.

Dr Aisenberg has been a consultant for Boehringer Ingelheim and Pfizer.

Suggested Reading

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